LUDWIG BOLTZMANN INSTITUTE Osteology

ANNUAL REPORT 2021

www.osteologie.lbg.ac.at

Contents

1 Abbreviations

AFF	Atypical Femoral Fractures
AFM	Atomic Force Microscopy
ALN	Alendronat
ALP	Alkaline Phosphatase
APECED	Autoimmune PolyEndocrinopathy-Candidiasis-Ectodermal Dystrophy
ATP	Adenosintriphosphat
BGLD	Blood Glucose Lowering Drugs
BMD	Bone Mineral Density
BMDD	Bone Mineralisation Density Distribution
BMU	Basic Multicellular Units
BRIL	Bone-Restricted IFITM-like
BV/TV	Bone Volume per Trabecular Volume
Ca	Calcium
CaMean	mittlere Ca-Konzentration
CaPeak	häufigste auftretende Ca-Konzentration
CaWidth	Peak-Breite der Knochenmineralisationsdichteverteilung
CaYoung	Mineral Content between the Labels
CD	Crohn's Disease
CKD	Chronic Kidney Disease
CKD-MBD	Chronic Kidney Disease–Mineral Bone Disorder
CLSM	Confocal Laser Scanning Microscopy
COL1A1	Collagen Type I alpha 1
COL1A2	Collagen Type I alpha 2
CRISPR/Cas	Clustered Regularly Interspaced Short Palindromic Repeats/ CRISPR-associated
CT	Computertomographie
DNA	Deoxyribonucleic Acid
DXA	Dual Energy X-Ray Absorptiometry
ECM	Extracellular Matrix
EDS	Ehlers Danlos Syndrome
EV	Extracellular Vesicles
FESEM	Field Emission Scanning Electron Microscope
FGF23	Fibroblast Growth Factor 23
FH	Femoral Head
Ficat	Classification of Osteonecrosis introduced by Dr Ficat
FLS	Fracture Liaison Service
FTIR	Fourier Transform Infrared
FTIRI	Fourier Transform Infrared Imaging
FWF	Fonds zur Förderung der wissenschaftlichen Forschung (Austrian Science Fund)
GACI	Generalised Arterial Calcification of Infancy
HbA1c	Hämoglobin A1 (Glykierung)
HF	Hip Fracture
HPP	Hypophosphatasia
HR-pQCT	High-Resolution peripheral Quantitative Computed Tomography
HRT	Hormonal Replacement Therapy
IFITM5	Interferon Induced Transmembrane Potein 5
IgG4-RD	Immunoglobulin G4 – Related Disease
ko	Knockout
LAP2α	Lamin-Associated Polypeptide 2 alpha
MC3T3-E1	Mouse Osteoblastic Cell Line

MDS	Myelodysplastic Syndromes
MIO	Male Idiopathic Osteoporosis
miRNA	microRNA
MMC	Mineral/Maturity/Crystallinity
MSCs	Mesenchymal Stem Cells
NIH	National Institutes of Health
NND	Nearest Neighbour Distance
OI	Osteogenesis imperfecta
OLCN	Osteocyte Lacuna Canaliculi Network
OLS	Osteocyte Lacunae Section
OPG	Osteoprotegerin
OVX	Ovariektomised
PEDF	(also SERPINF1) Pigment Epithelium-Derived Factor
PF	Pelvic Fracture
PLS3	Plastin 3
PMMA	Polymethyl Methacrylate
PPi	inorganic Pyrophosphate
PsA	Psoriatic Arthritis
PsO	Psoriasis
PTH	Parathyroid Hormone
qBEI	quantitative Backscattered Electron Imaging
RANKL	ReceRANKLptor Activator of NFkappa-B Ligand
RD	Rescue Diet
RNA	Ribonucleic Acid
ROD	Renal Osteodystrophy
RT-qPCR	Real-Time quantitative Polymerase Chain Reaction
SAM	Scanning Acoustic Microscope
SASAM	Saarland Scanning Acoustic Microscopy
SASP	Senescence-Associated Secretory Phenotype
SAXS	Small Angle X-Ray Scattering
SBA	Skin-Bone-Axis
SEM	Scanning Electron Microscope
SERS	Surface-Enhanced Raman Spectroscopy
SHAM	Placebo Surgery
SpA	Spondyloarthropathies
T2DM	Type 2 Diabetes Mellitus
TBS	Trabecular Bone Score
TERS	Tip-Enhanced Raman Spectroscopy
TMV	Turnover Mineralisation Volume
TNF	Tumour Necrosis Factor
TPTD	Teriparatide
ttw	tiptoe walking
VC-Epireg	Vitamin C Epigenetic Regulator
WNT1	Wnt family member 1
WT	Wild type
XLH	X-Linked Hypophosphatemia
ZOL	Zoledronic Acid

2 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) – now Austrian Social Health Insurance Fund (OEGK) and Ludwig Boltzmann Gesellschaft (LBG) at the Hanusch Hospital and the Trauma Centre Meidling, with Prof Klaus Klaushofer, MD, serving as the Scientific and Administrative Head until the end of 2018. As from 1st January 2019, he was succeeded by Assoc.Prof Jochen Zwerina, MD. A Board oversees the scientific and administrative activities of the LBIO with Board members representing the partner institutions (AUVA, OEGK, LBG). Special emphasis was placed on the organisation 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 centre within a multidisciplinary clinical network located at the two hospitals targeting diagnosis and treatment of bone and joint diseases.

2.1 Mission Statement

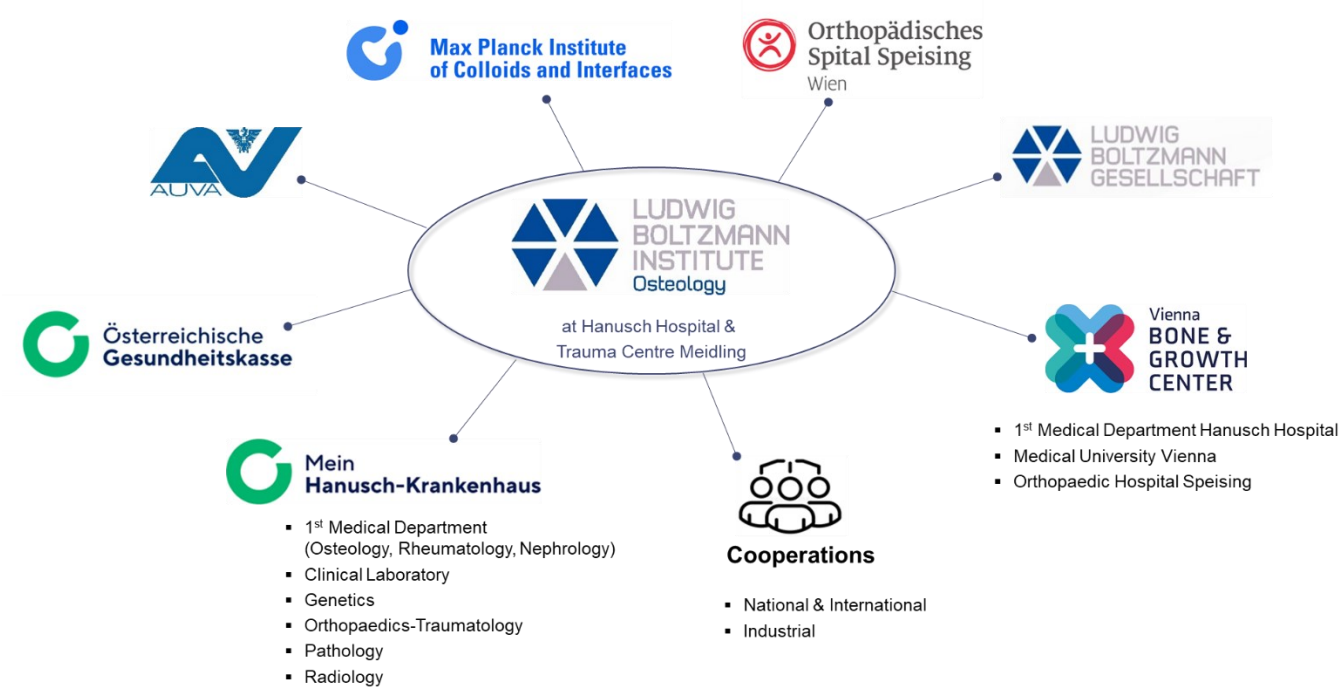
LBIO's **mission** is to achieve the highest level of scientific excellence through basic and clinical research, as well as the training of young scientists in clinical and experimental Osteology and the gender-neutral development of their careers.
LBIO's **goal** is the improvement of patient care.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

2.2 Organisation

External Organisation



Board members:
GD Mag Alexander Bernart (Präsident) (Allgemeine Unfallversicherungsanstalt)
Erol Holawatsch, MSc (Vizepräsident) (Österreichische Gesundheitskasse)
Mario Ferrari (Österreichische Gesundheitskasse)
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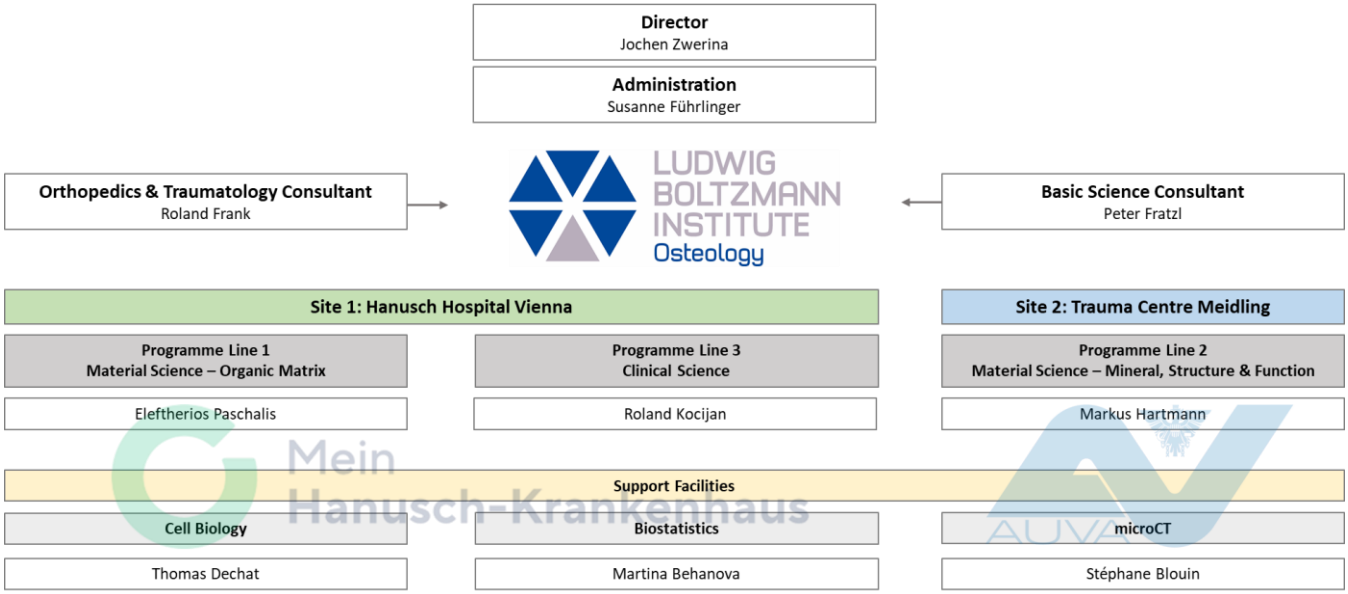
Senator Prof Mag Dr Günther Schön (Wirtschaftskammer Wien)
ÄD^{in} Dr$^{.in}$ Elisabeth Zwettler (Österreichische Gesundheitskasse)

Representatives of the Ludwig Boltzmann Society:
Mag.^{a} Claudia Lingner (Geschäftsführerin)
Dr Peter Mayrhofer (Bereichsleiter Medizin & Life Sciences)

Internal Organisation



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3 Co-operations

3.1 Partners

Allgemeine Unfallversicherungsanstalt und Traumazentrum Wien Meidling

Österreichische Gesundheitskasse

Hanusch-Krankenhaus

Ludwig Boltzmann Gesellschaft

3.2 Ongoing scientific co-operations

Amsterdam University Medical Center; Department of Rheumatology; Amsterdam; The Netherlands (Prof Willem Lems)

Austrian Cluster of Tissue Regeneration, Vienna, Austria (Assoc.Prof Sylvia Nürnberger)

Barmherzige Schwestern Hospital Vienna, II Medical Department, Vienna Austria (Prof Heinrich Resch, Dr Zora Messner)

Center Hospitalier Universitaire Vaudois (CHUV), Department of Nephrology, Lausanne, Switzerland (Prof Olivier Bonny)

Clinical Hospital of the Federal University of Parana, Department of Internal Medicine, Curitiba, PR, Brazil (Dr Carolina Moreira-Kulak)

Cochin Hospital, APHP-Centre, Department of Rheumatology, Paris, France (Prof Christian Roux)

Columbia University, Division of Endocrinology, New York, USA (Prof Elizabeth Shane, Prof David Dempster)

Creighton University School of Medicine, Department of Endocrinology, Omaha, USA (Prof. Robert R. Recker)

Eli Lilly and Company, Indianapolis, USA (Prof Fernando Marin, Prof Imre Pavo, Dr Liandong Ma, Dr Kathleen Taylor)

Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bone and Extracellular Matrix Branch, Bethesda, USA (Dr. Wayne Cabral, Dr. Joan Marini)

FH Wiener Neustadt, Biotechnical Processes, Tulln, Austria (Dr Katerina Prohaska)

Friedrich-Alexander University Erlangen-Nuremberg, Department of Internal Medicine 3, Erlangen, Germany (Prof. Georg Schett, Dr. David Simon)

Governing Body of Social Security Institutions, Vienna, Austria (Argumentation Group)

Harvard Medical School, Department of Orthopedic Surgery, Boston, USA (Prof Mary Bouxsein)

Harvard School of Dental Medicine, Division of Bone and Mineral Research, Oral Medicine, Infection and Immunity, Boston, USA (Prof Roland Baron)

Helsinki University Central Hospital and University of Helsinki, Department of Pediatrics, Helsinki, Finland (Prof. Outi Mäkitie, Dr. Pauliina Utriainen)

Image Biopsy Lab GmbH, Vienna, Austria (DI Richard Ljuhar, Mag. Philip Meier)

IMC FH Krems, Department of Life Sciences, Krems, Austria (Prof (FH) Christoph Wiesner)

Indiana University-Purdue University, Department of Biomedical Engineering, Indianapolis, USA (Prof. David Burr)

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Karolinska Institute, Department of Biosciences and Nutrition, Stockholm, Sweden (Prof. Maria Eriksson)

Kepler University Hospital, Department of Paediatrics and Adolescent Medicine, Linz, Austria (Prof Wolfgang Högler)

Kyowa Kirin Ltd, Galashiels, UK (Dr Paul Vandewalle)

Leiden University Medical Center, Department of Endocrinology, Leiden, The Netherlands (Prof. Sokrates Papapoulos)

Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria (Prof. Johannes Grillari)

Max-Planck-Institute of Colloids and Interfaces, Department of Biomaterials, Potsdam, Germany (Prof. Peter Fratzl, Dr. Richard Weinkamer)

Mayo Clinic, Department of Biochemistry and Molecular Biology, Rochester, USA (Dr. Roman Thaler)

McGill University Shriners Hospital for Children, Genetics Unit, Montreal, Canada (Prof. Frank Rauch, Prof. Francis H. Glorieux)

McMaster University, Divisions of Endocrinology and Metabolism and Geriatrics, Hamilton, Ontario, Canada (Prof Aliya Khan)

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

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TAmiRNA GmbH, Vienna, Austria (Dr. Matthias Hackl)

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University Medical Center and MVZ Endokrinologikum, Department of Internal Medicine and Endocrinology, Göttingen, Germany (Prof Heide Siggelkow)

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University of California, Molecular Biology Institute, Los Angeles, USA (Dr Stephen Young)

University of Florence, Department of Experimental and Clinical Biomedical Sciences, Florence, Italy (Prof Maria Luisa Brandi)

University of Kansas, Medical Center, Endocrinology, Diabetes and Clinical Pharmacology, Kansas, USA (Assistant Prof Eric Rush)

University of Liège, Mechanics of Biological and Bioinspired Materials Laboratory, Liège, Belgium (Prof Davide Ruffoni)

University of Pittsburgh, McGowan Institute for Regenerative Medicine, Pittsburgh, USA (Dr Konstantinos Verdelis)

4 Infrastructur/Methods

TECHNIQUE	OUTCOME
Light Microscopy/ Histomorphometry	Structural parameters, parameters of static bone formation and resorption, dynamic bone formation. Pathohistological diagnostic evaluation of bone biopsies in collaboration with the Department of Pathology at the Hanusch Hospital
Confocal Laser Scanning Microscopy (CLSM)	3D fluorescence imaging of labelled bone tissue, cellular structures & cytoskeletal architecture. Imaging of resorption lacunae in in-vitro assays. 3D imaging of the osteocyte lacuna-canalicular network
qBEI (quantitative backscattered electron imaging)	Bone mineral density distribution (BMDD) in a spatially resolved manner at the μm-range. Characteristics of osteocyte lacunae sections (OLS) including OLS-porosity, OLS-density, OLS-area, OLS-perimeter, OLS-aspect ratio and OLS-nearest neighbour distance. In combination with CLSM measurement of mineralisation kinetics (calcium concentration between the tetracycline double labels).
EDX (energy dispersive X-ray micro-analysis)	Elemental composition of bone (sensitivity of quantification 0.1%)
HR-BEI (high-resolution backscatter electron imaging)	Visualisation of bone matrix in nm-range (limit 4nm)
Scanning SAXS (Small-angle X-ray scattering) in coop. with Prof Fratzl	Information of bone mineral crystallites characteristics in a spatially resolved manner at the nanometer range.
Nanoindentation in coop. with Prof 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)	Mineral & organic matrix quantity and quality Tissue organisation Ability to image the whole bone biopsy surface All above outcomes may be obtained in both hard and soft tissues, with a spatial resolution of 1.1 μm
ATR-FTIR (Attenuated total reflectance Fourier transform infrared)	Analysis of extracellular matrix in *in situ* cell cultures.
RAMAN Spectroscopy	Mineral & organic matrix quantity and quality Tissue organisation and tissue water quantity All above outcomes may be obtained in both hard and soft tissues, with a spatial resolution of 0.6 μm
AFM-TERS (Atomic force microscopy coupled with tip-enhanced Raman spectroscopy)	Mineral & organic matrix quantity and quality Tissue organisation and tissue water quantity Ability to image the whole bone biopsy surface, albeit at much longer times compared to FTIRI Amino acid detection Tissue topography

	Mechanical outcomes such as elasticity All above outcomes may be obtained in both hard and soft tissues, in 3-D, with a spatial resolution of 10-100 µm
Micro-computed tomography (micro-CT) instrument shared with Prof Grillari	Architecture/structure of mineralised bone sample
CytoSMART Omni (Automated live-cell imaging bright-field microscope)	Long time (days up to weeks) high resolution phase contrast live cell imaging of whole cell cultures growing in various culture vessels (flasks, petri dishes and multi-well plates)

Further methods used in the Cell Biology unit comprise various cell culture techniques (e.g. cultivating cell lines as well as primary cells and stem cells, cell differentiation, cell transfection, genome editing using the CRISPR/Cas9 system, immunofluorescence microscopy) and molecular biology and biochemical techniques (e.g. cloning, expression analyses using quantitative RT-PCR and Affymetrix microarray analysis, Western Blot, immunoprecipitation, chromatin immunoprecipitation, expression and purification of recombinant proteins).

5 Closed projects and published manuscripts

5.1 Bone material properties and response to teriparatide in osteoporosis due to WNT1 and PLS3 mutations

Context: Patients with osteoporosis-associated WNT1 or PLS3 mutations have unique bone histomorphometric features and osteocyte-specific hormone expression patterns.
Objective: To investigate the effects of WNT1 and PLS3 mutations on bone material properties.
Design: Transiliac bone biopsies were evaluated by quantitative backscattered electron imaging, immunohistochemistry, and bone histomorphometry.
Setting: Ambulatory patients.
Patients: Three pediatric and eight adult patients with WNT1 or PLS3 mutations.
Intervention: Bone mineralization density distribution and osteocyte protein expression was evaluated in 11 patients and repeated in six patients who underwent repeat biopsy after 24 months of teriparatide treatment.
Main outcome measure: Bone mineralization density distribution and protein expression.
Results: Children with WNT1 or PLS3 mutations had heterogeneous bone matrix mineralization, consistent with bone modeling during growth. Bone matrix mineralization was homogenous in adults and increased throughout the age spectrum. Teriparatide had very little effect on matrix mineralization or bone formation in patients with WNT1 or PLS3 mutations. However, teriparatide decreased trabecular osteocyte lacunae size and increased trabecular bone FGF23 expression.
Conclusion: The contrast between preserved bone formation with heterogeneous mineralization in children and low bone turnover with homogenous bone mineral content in adults suggests that WNT1 and PLS3 have differential effects on bone modeling and remodeling. The lack of change in matrix mineralization in response to teriparatide, despite clear changes in osteocyte lacunae size and protein expression, suggests that altered WNT1 and PLS3 expression may interfere with coupling of osteocyte, osteoblast, and osteoclast function. Further studies are warranted to determine the mechanism of these changes.

Bone 146:115900 IF 4.398 (1577)

5.2 Glucose metabolism after kidney transplantation: Insulin release and sensitivity with tacrolimus- versus belatacept-based immunosuppression

Letter to the editor.

Am J Kidney Dis 77:462-4 8.860 (1578)

5.3 Circulating miRNAs in bone health and disease

microRNAs have evolved as important regulators of multiple biological pathways essential for bone homeostasis, and microRNA research has furthered our understanding of the mechanisms underlying bone health and disease. This knowledge, together with the finding that active or passive release of microRNAs from cells into the extracellular space enables minimal-invasive detection in biofluids (circulating miRNAs), motivated researchers to explore microRNAs as biomarkers in several pathologic conditions, including bone diseases. Thus, exploratory studies in cohorts representing different types of bone diseases have been performed. In this review, we first summarize important molecular basics of microRNA function and release and provide recommendations for best (pre-)analytical practices and documentation standards for circulating microRNA research required for generating high quality data and ensuring reproducibility of results. Secondly, we review how the genesis of bone-derived circulating microRNAs via release from osteoblasts and osteoclasts could contribute to the communication between these cells. Lastly, we summarize evidence from clinical research studies that have investigated the clinical utility of microRNAs as biomarkers in musculoskeletal disorders. While previous reviews have mainly focused on diagnosis of primary osteoporosis, we have also included studies exploring the

utility of circulating microRNAs in monitoring anti-osteoporotic treatment and for diagnosis of other types of bone diseases, such as diabetic osteopathy, bone degradation in inflammatory diseases, and monogenetic bone diseases.

Bone 145:115787 4.398 (1579)

5.4 Variants in PCSK7, PNPLA3 and TM6SF2 are risk factors for the development of cirrhosis in hereditary haemochromatosis

Background: Cirrhosis develops in <10% of individuals homozygous for the C282Y variant in the homeostatic iron regulator (HFE) gene. Carriage of PCSK7:rs236918 is associated with an increased risk of cirrhosis in this population.

Aim: To determine if genetic variants significantly associated with the risk of alcohol- and NAFLD-related cirrhosis also modulate the cirrhosis risk in C282Y homozygotes.

Methods: Variants in PCSK7, PNPLA3, TM6SF2, MBOAT7 and HSD17B13 were genotyped in 1319 C282Y homozygotes, from six European countries, of whom 171 (13.0%) had cirrhosis. Genotypic and allelic associations with the risk for developing cirrhosis were assessed, adjusting for age and sex. Fixed effects meta-analyses of the adjusted summary data for each country were performed. Post hoc association testing was undertaken in the 131 (76.6%) cases and 299 (26.0%) controls with available liver histology.

Results: Significant associations were observed between PCSK7:rs236918 (OR = 1.52 [95% CI 1.06-2.19]; P = 0.022; I2 = 0%); PNPLA3:rs738409 (OR = 1.60 [95% CI 1.22-2.11]; P = 7.37 × 10-4 ; I2 = 45.5%) and TM6SF2:rs58542926 (OR = 1.94 [95% CI 1.28-2.95]; P = 1.86 × 10-3 ; I2 = 0%) and the cirrhosis risk in C282Y homozygotes. These findings remained significant in the subpopulation with available liver histology. The population-attributable fractions were 5.6% for PCSK7:rs236918, 13.8% for PNPLA3:rs738409, 6.5% for TM6SF2:rs58542926 and 24.0% for carriage of all three variants combined.

Conclusions: The risk of cirrhosis associated with carriage of PCSK7:rs236918 was confirmed in this much larger population of C282Y homozygotes. In addition, PNPLA3:rs738409 and TM6SF2:rs58542926 were established as significant additional risk factors. More detailed genetic testing of C282Y homozygotes would allow risk stratification and help guide future management.

Aliment Pharmacol Ther 53:830-43 IF 8.171 (1580)

5.5 Biomarker profiles of endothelial activation and dysfunction in rare systemic autoimmune diseases: implications for cardiovascular risk

Objectives: Vasculopathy is an important hallmark of systemic chronic inflammatory connective tissue diseases (CICTD) and is associated with increased cardiovascular risk. We investigated disease-specific biomarker profiles associated with endothelial dysfunction, angiogenic homeostasis and (tissue) inflammation, and their relation to disease activity in rare CICTD.

Methods: A total of 38 serum proteins associated with endothelial (dys)function and inflammation were measured by multiplex-immunoassay in treatment-naive patients with localized scleroderma (LoS, 30), eosinophilic fasciitis (EF, 8) or (juvenile) dermatomyositis (34), 119 (follow-up) samples during treatment, and 65 controls. Data were analysed by unsupervised clustering, Spearman correlations, non-parametric t test and ANOVA.

Results: The systemic CICTD, EF and dermatomyositis, had distinct biomarker profiles, with 'signature' markers galectin-9 (dermatomyositis) and CCL4, CCL18, CXCL9, fetuin, fibronectin, galectin-1 and TSP-1 (EF). In LoS, CCL18, CXCL9 and CXCL10 were subtly increased. Furthermore, dermatomyositis and EF shared upregulation of markers related to interferon (CCL2, CXCL10), endothelial activation (VCAM-1), inhibition of angiogenesis (angiopoietin-2, sVEGFR-1) and inflammation/leucocyte chemo-attraction (CCL19, CXCL13, IL-18, YKL-40), as well as disturbance of the Angiopoietin-Tie receptor system and VEGF-VEGFR system. These profiles were related to disease activity, and largely normalized during treatment. However, a subgroup of CICTD patients showed continued elevation of CXCL10, CXCL13, galectin-9, IL-18, TNFR2,

VCAM-1, and/or YKL-40 during clinically inactive disease, possibly indicating subclinical interferon-driven inflammation and/or endothelial dysfunction.
Conclusion: CICTD-specific biomarker profiles revealed an anti-angiogenic, interferon-driven environment during active disease, with incomplete normalization under treatment. This warrants further investigation into monitoring of vascular biomarkers during clinical follow-up, or targeted interventions to minimize cardiovascular risk in the long term.

Rheumatology (Oxford) 60:785-801 IF 7:580 (1581)

5.6 Poor adherence to parenteral osteoporosis therapies during COVID-19 pandemic

The COVID-19 pandemic was first recognized in Austria in February 2020, followed by a first extensive lockdown in March and April 2020. In that time, there was limited access to outpatient clinics. We present the national data of the DVSV (Dachverband der Sozialversicherungsträger—the umbrella association of all social insurance companies in Austria). Data are based on filled prescriptions for denosumab, zoledronic acid (ZOL) and ibandronic acid (IBA) covering a period from January 2017 until September 2020. The results showed a continuous increase of DMAB prescriptions over the last 2 years with a remarkable decrease only during the first COVID-19-lockdown in March and April 2020. Thus, a 22 and 23% reduction as compared with 6 months prior for DMAB prescriptions were observed. Moreover, also the number of prescriptions for (ZOL) was significantly lower in the 2 months of the first lockdown compared with 12 months prior (−36 and −49%, respectively). The number of filled prescriptions for intravenous IBA was decreased by 23 and 18% (when compared with the mean number of filled prescriptions of the previous 12 months). Especially patients on Denosumab should receive their treatment on time. That also applies to patients in nursing homes and patients at higher risk for COVID-19 infections. As for rheumatological treatments, patients could be instructed about denosumab self-administration [7]. Telemedicine including telephone and video consultation may increase the adherence to osteoporosis treatments [8]. It is currently unclear if the lower rate of DMAB prescriptions is also associated with a higher rate of rebound-associated vertebral fractures. Future studies should investigate the impact of repeated lockdowns on DMAB treatment adherence and clinical outcomes.

Arch Osteoporos 16:46 IF 2.617 (1582)

5.7 Interplay between mineral crystallinity and mineral accumulation in health and postmenopausal osteoporosis

Osteoporosis is characterized by an imbalance between bone formation and resorption rates, resulting in bone loss. For ethical reasons, effects of antiosteoporosis drugs are compared against patients receiving vitamin D and calcium supplementation which is a mild antiresorptive regimen. Bone formation may be resolved into two phases: the initial formation of mineral crystals (primary nucleation) and the subsequent mineral accumulation (secondary nucleation and mineral growth) on them. In this study, we used Raman microspectroscopic analysis of iliac crest biopsies from healthy females (N = 108), postmenopausal osteoporosis patients receiving vitamin D and calcium supplementation (PMOP-S; N = 66), and treatment-naïve postmenopausal osteoporosis patients (PMOP-TN; N = 12) to test the hypothesis that at forming trabecular surfaces, mineral maturity / crystallinity of the youngest crystallites associates with the amount of subsequent mineral accumulation. The surfaces of analysis were chosen based on the presence of fluorescent double labels, defining three distinct tissue ages. The results indicated that when adjusted for age and tissue age, there were no differences in amount of mineral formed between healthy females and either PMOP-S or PMOP-TN, while both PMOP-S and PMOP-TN had larger crystallites compared to healthy females. Moreover, significant differences existed between PMOP-S and PMOP-TN in size of initial crystals formed as well as rate of mineral accumulation and maturation. These findings suggest an additional mechanism that may contribute to the decreased mineral content

evident in PMOP, and provide a potential target for the development of new interventions. STATEMENT OF SIGNIFICANCE: We used Raman microspectroscopic analysis of iliac crest biopsies from healthy females and postmenopausal osteoporosis patients (PMOP) receiving placebo to test the hypothesis that at forming trabecular surfaces, mineral maturity / crystallinity (MMC) of the youngest crystallites associates with the amount of subsequent mineral accumulation. This can affect bone mechanical properties as larger crystallites have been shown to result in compromised mechanical attributes; and larger crystallites grow slower compared to smaller ones. The results of the present analysis indicate that increased MMC of the youngest formed mineral may contribute to the bone mineral loss evident in PMOP and the accompanying increased fracture risk independently of bone turnover rate.

Acta Biomater 124:374-81 IF 8.947 (1583)

5.8 Mineral and organic matrix composition at bone forming surfaces in postmenopausal women with osteoporosis treated with either teriparatide or zoledronic acid

The ability of bone to resist fracture is dependent on the composite nature of its mineral and organic matrix content. Teriparatide (TPTD) and zoledronic acid (ZOL) are approved anabolic and antiresorptive therapies, respectively, to reduce fracture risk in women with postmenopausal osteoporosis. In the SHOTZ study, postmenopausal women with osteoporosis were treated with TPTD (20 μg daily, subcutaneous) or ZOL (5 mg/year, intravenous infusion) for 24 months. Iliac crest biopsies were obtained at 6 months and again at 24 months from approximately one third of the original study cohort. To investigate the early effects of these two drugs on the quality of newly formed bone, we used vibrational spectroscopic techniques to analyze tetracycline-labelled transiliac biopsies obtained from participants at the 6-month time point. Raman spectra were acquired at forming trabecular and intra-cortical surfaces (identified by fluorescent double labels), to determine mineral, organic matrix, glycosaminoglycan, and tissue water content, as well as mineral maturity/crystallinity at three specific tissue ages (1-5, 15, and ≥25 days). Fourier transformed infrared microspectroscopy was used to determine pyridinoline/divalent collagen cross-link ratios. At 6 months, treatment with TPTD versus ZOL resulted in lower mineral and higher organic matrix content, increased tissue water content, and lower mineral/matrix, mineral maturity/crystallinity, glycosaminoglycan content, and pyridinoline/divalent enzymatic collagen cross-link ratio. Our results suggest that TPTD and ZOL have differential effects on material properties of newly formed bone at individual remodeling sites, highlighting their different mechanisms of action.

Bone 145:115848 IF 4.398 (1584)

5.9 Type I Interferon as cardiovascular risk factor in systemic and cutaneous lupus erythematosus: A systematic review

Objective: Patients with systemic lupus erythematosus (SLE) have a high burden of cardiovascular disease (CVD) of multifactorial origin. The aim of this systematic review is to analyze the role of the interferon I (IFN-I) signature and fibroblast growth factor-23 (FGF-23) in patients with SLE or cutaneous lupus erythematosus (CLE) herein.

Materials and methods: We conducted a systematic literature search in PubMed and Scopus using keywords for major adverse cardiovascular events (MACE) and intermediate outcomes (endothelial dysfunction, subclinical atherosclerosis, platelet activation) associated with IFN-I or FGF-23 in patients with SLE and CLE.

Results: 4745 citations were screened, of which 12 studies were included. IFN-I was associated with MACE in two third of the studies and the association was strongest for cardiac events. An association of IFN-I was found in all studies investigating impaired vascular function, but only in 50% (respectively 40%) of reports examining the relation of IFN-I and platelet activation (respectively subclinical atherosclerosis). Altogether the reports were of variable bias and quality

due to high variability of examined IFN-I biomarkers and inconsistent results for different outcome measures. No studies investigating the cardiovascular risk of circulating IFN-I in CLE, nor FGF-23 in SLE or CLE were found.
Conclusion: Clinical studies measuring the association between IFN-I and direct / intermediate measures of CVD are rare and ambiguous in SLE and nonexistent in CLE, hampering a definite conclusion.

Autoimmun Rev 17:102794 IF 9.754 (1585)

5.10 Skeletal pathology and bone mineral density changes in wild muskrats (Ondatra zibethicus) and red squirrels (Tamiasciurus hudsonicus) inhabiting arsenic polluted areas of Yellowknife, Northwest Territories (Canada): A radiographic densitometry study

The City of Yellowknife is a known hotspot of arsenic contamination and there is a growing body of evidence suggesting that local wildlife in the vicinity of the abandoned Giant Mine site may be at risk of decreased bone mineralization and various bone disorders. The purpose of this study was to preliminarily measure bone mineral density (BMD) changes and investigate the incidence, pattern, and severity of bone lesions in wild muskrats and red squirrels breeding in three (3) catchment areas at different distances from the Giant Mine Site in Yellowknife, Northwest Territories (Canada): ~2 km (location 1), ~18 km (location 2), and ~40-100 km (location 3). Full femoral bones of 15 muskrats and 15 red squirrels were collected from the three sampling locations (5 from each location) and subjected to radiographic analysis and densitometric measurements. The patterns and severities of bone lesions, including changes in bone mineral density, were evaluated and compared between groups. As levels were significantly higher in the bones of muskrats caught from location 1 and 2, relative to location 3. Further, As and Cd levels were significantly higher in the bones of squirrels caught from locations 1 and 2 relative to squirrels caught from location 3. The preliminary results from bones revealed that radiographic abnormalities such as bone rarefaction, osteopenia, and thinning of the femoral shafts with significant ossific cystic lesions and bowing were the most common skeletal pathologies found in bones of red squirrels from the three locations. Radiographic appearances of massive sclerosis and dysplasia, including severe osteocondensation and osteopathia striata-like abnormalities, were found in the bones of muskrats from all the sampling locations. Densitometric evaluation showed no significant differences between the three locations in the bone parameters measured. However, there was a statistically significant correlation between As content in the bones of muskrats and percent fat content in the femur samples, which suggests that accumulation of As could have been a causal factor for a change in percent fat in femurs of muskrats.

Ecotoxicol Environ Saf 208:111721 IF 6.291 (1586)

5.11 Osteoconductive properties of a volume-stable collagen matrix in rat calvaria defects: A pilot study

Volume-stable collagen matrices (VSCM) are conductive for the connective tissue upon soft tissue augmentation. Considering that collagen has osteoconductive properties, we have investigated the possibility that the VSCM also consolidates with the newly formed bone. To this end, we covered nine rat calvaria circular defects with a VSCM. After four weeks, histology, histomorphometry, quantitative backscattered electron imaging, and microcomputed tomography were performed. We report that the overall pattern of mineralization inside the VSCM was heterogeneous. Histology revealed, apart from the characteristic woven bone formation, areas of round-shaped hypertrophic chondrocyte-like cells surrounded by a mineralized extracellular matrix. Quantitative backscattered electron imaging confirmed the heterogenous mineralization occurring within the VSCM. Histomorphometry found new bone to be 0.7 mm2 (0.01 min; 2.4 max), similar to the chondrogenic mineralized extracellular matrix with 0.7 mm2 (0.0 min; 4.2 max). Microcomputed tomography showed the overall mineralized tissue in the defect to be 1.6 mm3 (min 0.0; max 13.3). These

findings suggest that in a rat cranial defect, VSCM has a limited and heterogeneous capacity to support intramembranous bone formation but may allow the formation of bone via the endochondral route.

Biomedicines 9:732 IF 6.081 (1587)

5.12 LAP2alpha maintains a mobile and low assembly state of A-type lamins in the nuclear interior

Lamins form stable filaments at the nuclear periphery in metazoans. Unlike B-type lamins, lamins A and C localize also in the nuclear interior, where they interact with lamin-associated polypeptide 2 alpha (LAP2α). Using antibody labeling, we previously observed a depletion of nucleoplasmic A-type lamins in mouse cells lacking LAP2α. Here, we show that loss of LAP2α actually causes formation of larger, biochemically stable lamin A/C structures in the nuclear interior that are inaccessible to lamin A/C antibodies. While nucleoplasmic lamin A forms from newly expressed pre-lamin A during processing and from soluble mitotic lamins in a LAP2α-independent manner, binding of LAP2α to lamin A/C during interphase inhibits formation of higher order structures, keeping nucleoplasmic lamin A/C in a mobile state independent of lamin A/C S22 phosphorylation. We propose that LAP2α is essential to maintain a mobile lamin A/C pool in the nuclear interior, which is required for proper nuclear functions.

eLife 10:e63476 IF 7.080 (1588)

5.13 Dual targeting of salt inducible kinases and CSF1R uncouples bone formation and bone resorption

Bone formation and resorption are typically coupled, such that the efficacy of anabolic osteoporosis treatments may be limited by bone destruction. The multi-kinase inhibitor YKL-05-099 potently inhibits salt inducible kinases (SIKs) and may represent a promising new class of bone anabolic agents. Here we report that YKL-05-099 increases bone formation in hypogonadal female mice without increasing bone resorption. Postnatal mice with inducible, global deletion of SIK2 and SIK3 show increased bone mass, increased bone formation, and, distinct from the effects of YKL-05-099, increased bone resorption. No cell-intrinsic role of SIKs in osteoclasts was noted. In addition to blocking SIKs, YKL-05-099 also binds and inhibits CSF1R, the receptor for the osteoclastogenic cytokine M-CSF. Modeling reveals that YKL-05-099 binds to SIK2 and CSF1R in a similar manner. Dual targeting of SIK2/3 and CSF1R induces bone formation without concomitantly increasing bone resorption and thereby may overcome limitations of most current anabolic osteoporosis therapies.

eLife 10:e67772 IF 7.080 (1589)

5.14 Single high-dose peroral caffeine intake inhibits ultraviolet radiation-induced apoptosis in human lens epithelial cells in vitro

Purpose: The aim of the present study was to determine whether caffeine concentrations in human lens epithelial cells (LECs) achieved from acute peroral caffeine intake inhibit ultraviolet radiation-induced apoptosis in vitro.

Methods: Patients were planned for cataract surgery of both eyes with a caffeine abstinence of 2 weeks in total, starting 1 week before surgery of the first eye. The second eye was scheduled 1 week after the first eye. At the day of the second eye surgery, patients were given coffee containing 180 mg caffeine shortly before surgery. Lens capsules including LEC, harvested after capsulorhexis, were transferred to a cell culture dish and immediately exposed to close to threshold ultraviolet radiation (UVR). At 24 hr after UVR exposure, apoptotic LECs were analysed by TdT-mediated dUTP-biotin nick end labeling (TUNEL) staining.

Results: TUNEL-positive cells were detected in UVR-exposed lens capsules both after caffeine intake and in controls. The mean difference in TUNEL-positive cells between caffeine intake and contralateral controls (no caffeine) resulted in a 95% CI 15.3 ± 10.4% (degrees of freedom: 16).

Conclusion: Peroral caffeine consumption significantly decreased UVR-induced apoptosis in LEC supporting epidemiological findings that caffeine delays the onset of cataract.

Acta Ophthalmol 99:e587-93 IF 3.761 (1590)

5.15 Effects of childhood-onset SLE on academic achievements and employment in adult life

Objective: Long-term outcome data in adults with childhood-onset systemic lupus erythematosus (cSLE) are limited. Here, we report the effects of cSLE on education, vocation, and employment in a large cohort of adults with cSLE.

Methods: Patients were seen for a single study visit comprising a structured history and physical examination. Medical records were retrieved to supplement information obtained during the study visit. Education and employment status were assessed by questionnaires. Health-related quality of life (HRQOL) was measured with the 36-Item Short Form Health Survey (SF-36).

Results: One hundred six patients with cSLE (93% female, 73% White), with a median disease duration of 20 years, completed the visit and questionnaires. Almost all patients stated that cSLE had influenced their education, but the level of completed education was similar to the general Dutch population. Half of the patients had adjusted their vocational choice due to the disease. Still, 44% of patients who had finished education did not have a paid job. Of the employed patients, 61% worked part time. Disease damage was equally prevalent in patients with and without paid employment. A high percentage of patients (51%) were declared work disabled, due to disease damage. Patients who did not have paid employment were often work disabled. Both had a negative effect on HRQOL.

Conclusion: The effect of cSLE on academic achievements and employment is substantial, despite patients adjusting their educational and vocational choices. To optimize participation in the community, ongoing support is necessary, not only to help patients find suitable education and vocations but also to offer guidance regarding potential adjustments during their career.

J Rheumatol 48:915-23 IF 3.350 (1591)

5.16 Longitudinal changes of circulating miRNAs during bisphosphonate and teriparatide treatment in an animal model of postmenopausal osteoporosis

MicroRNAs regulate bone homeostasis, and circulating microRNAs have been proposed as novel bone biomarkers. The effect of anti-osteoporotic treatment on circulating microRNAs has not been described in detail. Therefore, we performed a comprehensive analysis of microRNA serum levels in ovariectomized (OVX) and sham-operated (SHAM) rats over 12 weeks of antiresorptive or osteoanabolic treatment. Forty-two Sprague Dawley rats underwent SHAM surgery (n = 10) or ovariectomy (n = 32). After 8 weeks, OVX rats were randomized to antiresorptive treatment with zoledronate (n = 11), osteoanabolic treatment with teriparatide (n = 11), or vehicle treatment (n = 10). Serum samples were collected at weeks 8, 12, 16, and 20 after surgery. A total of 91 microRNAs were analyzed by RT-qPCR in serum samples collected at week 20. Based on the results, 29 microRNAs were selected for longitudinal analysis at all four study time points. Changes in bone mineral density and microstructure were followed up by in vivo micro-CT and ex vivo nano-CT. Ovariectomy resulted in the loss of trabecular bone, which was reversed by osteoanabolic and antiresorptive treatment. Differential expression analysis identified 11 circulating miRNAs that were significantly regulated after treatment. For example, miR-107 and miR-31-5p increased in vehicle-treated OVX animals, whereas they decreased during teriparatide treatment. Additional miRNAs were identified that showed significant correlations to bone microstructure or bone miRNA expression, including miR-203a-3p, which exhibited a significant negative correlation to vertebral and tibial trabecular bone volume fraction (%). Longitudinal analysis confirmed eight microRNAs with significant changes in serum over time that were prevented by teriparatide and zoledronate treatment (miR-34a-5p, miR-31-5p, miR-30d-3p, miR-378a-5p) or teriparatide treatment only (miR-375-3p, miR-183-5p, miR-203a-3p, miR-203b-3p). Gene target network

analysis identified WNT and Notch signaling as the main signaling pathways controlled by these miRNAs. Thus, ovariectomy results in time-dependent deregulation of circulating miRNAs compared with SHAM animals. Anti-osteoporotic treatments can rescue this effect, showing that bone-related miRNAs might act as novel biomarkers for treatment monitoring.

J Bone Miner Res 36:1131-44 IF 6.741 (1592)

5.17 Analysis of bone architecture using fractal-based TX-Analyzer™ in adult patients with osteogenesis imperfecta

Background: Osteogenesis imperfecta (OI) is a rare genetic disorder characterized by impaired bone quality and quantity. Established imaging techniques have limited reliability in OI. The TX-Analyzer™ is a new, fractal-based software allowing a non-invasive assessment of bone structure based on conventional radiographs. We explored whether the TX-Analyzer™ can discriminate OI patients and healthy controls. Furthermore, we investigated the correlation between TX-Analyzer™ parameters and (i) bone mineral density (BMD) by Dual Energy X-ray Absorptiometry (DXA), (ii) trabecular bone score (TBS), and (iii) bone microstructure by high-resolution peripheral quantitative computed tomography (HR-pQCT).

Material and methods: Data of 29 adult OI patients were retrospectively analyzed. Standard radiographs of the thoracic and lumbar spine were evaluated using the TX-Analyzer™. Bone Structure Value (BSV), Bone Variance Value (BVV), and Bone Entropy Value (BEV) were measured at the vertebral bodies T7 to L5. Data were compared to a healthy, age- and gender-matched control group (n = 58). BMD by DXA, TBS, and trabecular bone microstructure by means of HR-pQCT were correlated to TX-Analyzer™ parameters in OI patients. The accuracy of the TX-Analyzer™ parameters in detecting OI was assessed with area under curve (AUC) analysis of receiver operating characteristic (ROC).

Results: BEV of the thoracic and the lumbar spine were significantly lower in OI patients compared to controls (both $p < 0.001$). BEV of the thoracic spine was significantly correlated to TBS ($\rho = 0.427$, $p = 0.042$) as well as trabecular number (Tb.N) at the radius ($\rho = 0.603$, $p = 0.029$) and inhomogeneity of the trabecular network (Tb.1/N.SD) at the radius ($\rho = -0.610$, $p = 0.027$), when assessed by HR-pQCT. No correlations were found between BEV and BMD by DXA. BEV of the thoracic and the lumbar spine had an AUC of 0.81 (95% confidence interval [CI] 0.67-0.94, $p < 0.001$) and 0.73 (95% CI 0.56-0.89, $p = 0.008$), respectively. BSV and BVV did not differ between OI patients and controls.

Conclusion: The software TX-Analyzer™ is able to discriminate patients with OI from healthy controls. ROC curves of BEV values suggest a suitable clinical applicability. Low to no correlations with conventional methods suggest, that the TX-Analyzer™ may indicate a new and independent examination tool in OI.

Bone 147:115915 IF 4.398 (1593)

5.18 The doubled burden of diabetic bone disease: hip fracture and post-hip fracture mortality

Objective: Patients with diabetes have an increased risk of osteoporosis and shorter life expectancy. Hip fracture (HF) is the most serious consequence of osteoporosis and is associated with increased mortality risk. We aimed to assess the association of antidiabetic medications with HF and the post-hip fracture mortality risk among diabetic patients ≥50 years.

Design: In this nationwide case-control study 53 992 HF cases and 112 144 age-, sex- and region-matched non-hip fracture controls were analyzed. A cohort of hip-fractured diabetic patients were followed-up for an all-cause mortality.

Methods: We defined three groups of diabetic patients based on a prescription of antidiabetic medications: group 1 treated with insulin monotherapy (G1DM), group 2 (G2DM) treated with blood glucose-lowering drugs (BGLD) only, group 3 on a combined BGLD and insulin therapy (G3DM). We applied logistic regression and Cox regression.

Results: We identified 2757 G1DM patients, 15 310 G2DM patients, 3775 G3DM patients and 144 294 patients without any antidiabetic treatment. All three groups of diabetic patients had increased odds of HF compared to controls. G1DM patients aged 50-64 years (aOR: 4.80, 95% CI: 3.22-7.17) and G3DM patients (aOR: 1.39, 95% CI: 1.02-1.88) showed the highest HF odds, whereas G2DM patients had 18% decrease in HF odds than their non-diabetic controls (aOR: 0.82, 95% CI: 0.69-0.99). All diabetic patients had increased post-hip fracture mortality risk compared to non-diabetic controls. The highest mortality hazard was observed in G1DM patients, being greater for women than men (HR: 1.71, 95% CI: 1.55-1.89 and HR: 1.44, 95% CI: 1.27-1.64, respectively).
Conclusions: Antidiabetic medications increase the probability of HF. Diabetic patients, who sustained HF have a higher mortality risk than non-diabetic patients.

J Endocrinol 184:627-36 IF 6.664 (1594)

5.19 Hypermineralization of hearing-related bones by a specific osteoblast subtype

Auditory ossicles in the middle ear and bony labyrinth of the inner ear are highly mineralized in adult mammals. Cellular mechanisms underlying formation of dense bone during development are unknown. Here, we found that osteoblast-like cells synthesizing highly mineralized hearing-related bones produce both type I and type II collagens as the bone matrix, while conventional osteoblasts and chondrocytes primarily produce type I and type II collagens, respectively. Furthermore, these osteoblast-like cells were not labeled in a "conventional osteoblast"-specific green fluorescent protein (GFP) mouse line. Type II collagen-producing osteoblast-like cells were not chondrocytes as they express osteocalcin, localize along alizarin-labeled osteoid, and form osteocyte lacunae and canaliculi, as do conventional osteoblasts. Auditory ossicles and the bony labyrinth exhibit not only higher bone matrix mineralization but a higher degree of apatite orientation than do long bones. Therefore, we conclude that these type II collagen-producing hypermineralizing osteoblasts (termed here auditory osteoblasts) represent a new osteoblast subtype.

J Bone Miner Res 36:1535-47 IF 6.741 (1595)

5.20 Increased osteocyte lacunae density in the hypermineralized bone matrix of children with osteogenesis imperfecta type I

Osteocytes are terminally differentiated osteoblasts embedded within the bone matrix and key orchestrators of bone metabolism. However, they are generally not characterized by conventional bone histomorphometry because of their location and the limited resolution of light microscopy. OI is characterized by disturbed bone homeostasis, matrix abnormalities and elevated bone matrix mineralization density. To gain further insights into osteocyte characteristics and bone metabolism in OI, we evaluated 2D osteocyte lacunae sections (OLS) based on quantitative backscattered electron imaging in transiliac bone biopsy samples from children with OI type I (n = 19) and age-matched controls (n = 24). The OLS characteristics were related to previously obtained, re-visited histomorphometric parameters. Moreover, we present pediatric bone mineralization density distribution reference data in OI type I (n = 19) and controls (n = 50) obtained with a field emission scanning electron microscope. Compared to controls, OI has highly increased OLS density in cortical and trabecular bone (+50.66%, +61.73%; both $p < 0.001$), whereas OLS area is slightly decreased in trabecular bone (-10.28%; $p = 0.015$). Correlation analyses show a low to moderate, positive association of OLS density with surface-based bone formation parameters and negative association with indices of osteoblast function. In conclusion, hyperosteocytosis of the hypermineralized OI bone matrix associates with abnormal bone cell metabolism and might further impact the mechanical competence of the bone tissue.

Int J Mol Sci 22:4508 IF 5.923 (1596)

5.21 Quantitative backscattered electron imaging of bone using a thermionic or a field emission electron source

Quantitative backscattered electron imaging is an established method to map mineral content distributions in bone and to determine the bone mineralization density distribution (BMDD). The method we applied was initially validated for a scanning electron microscope (SEM) equipped with a tungsten hairpin cathode (thermionic electron emission) under strongly defined settings of SEM parameters. For several reasons, it would be interesting to migrate the technique to a SEM with a field emission electron source (FE-SEM), which, however, would require to work with different SEM parameter settings as have been validated for DSM 962. The FE-SEM has a much better spatial resolution based on an electron source size in the order of several 100 nanometers, corresponding to an about [Formula: see text] to [Formula: see text] times smaller source area compared to thermionic sources. In the present work, we compare BMDD between these two types of instruments in order to further validate the methodology. We show that a transition to higher pixel resolution (1.76, 0.88, and 0.57 µm) results in shifts of the BMDD peak and BMDD width to higher values. Further the inter-device reproducibility of the mean calcium content shows a difference of up to 1 wt% Ca, while the technical variance of each device can be reduced to [Formula: see text] wt% Ca. Bearing in mind that shifts in calcium levels due to diseases, e.g., high turnover osteoporosis, are often in the range of 1 wt% Ca, both the bone samples of the patients as well as the control samples have to be measured on the same SEM device. Therefore, we also constructed new reference BMDD curves for adults to be used for FE-SEM data comparison.

Calcif Tissue Int 109:190-202 IF 4.333 (1597)

5.22 3D interrelationship between osteocyte network and forming mineral during human bone remodeling

During bone remodeling, osteoblasts are known to deposit unmineralized collagenous tissue (osteoid), which mineralizes after some time lag. Some of the osteoblasts differentiate into osteocytes, forming a cell network within the lacunocanalicular network (LCN) of bone. To get more insight into the potential role of osteocytes in the mineralization process of osteoid, sites of bone formation are three-dimensionally imaged in nine forming human osteons using focused ion beam-scanning electron microscopy (FIB-SEM). In agreement with previous observations, the mineral concentration is found to gradually increase from the central Haversian canal toward pre-existing mineralized bone. Most interestingly, a similar feature is discovered on a length scale more than 100-times smaller, whereby mineral concentration increases from the LCN, leaving around the canaliculi a zone virtually free of mineral, the size of which decreases with progressing mineralization. This suggests that the LCN controls mineral formation but not just by diffusion of mineralization precursors, which would lead to a continuous decrease of mineral concentration from the LCN. The observation is, however, compatible with the codiffusion and reaction of precursors and inhibitors from the LCN into the bone matrix.

Adv Healthcare Mater 10:e2100113 IF 9.933 (1598)

5.23 Lugol's solution but not formaldehyde affects bone microstructure and bone mineral density parameters at the insertion site of the rotator cuff in rats

Background: This study aimed to investigate whether rodent shoulder specimens fixed in formaldehyde for histological and histomorphometric investigations and specimens stained using Lugol's solution for soft tissue visualization by micro-computed tomography (microCT) are still eligible to be used for bone architecture analysis by microCT.

Methods: In this controlled laboratory study, 11 male Sprague-Dawley rats were used. After sacrifice and exarticulation both shoulders of healthy rats were assigned into three groups: (A) control group (n = 2); (B) formaldehyde group (n = 4); (C) Lugol group (n = 5). Half of the specimens of groups B and C were placed in a 4% buffered formaldehyde or Lugol's solution for 24 h, whereas the contralateral sides and all specimens of group A were stored without any

additives. MicroCT of both sides performed in all specimens focused on bone mineral density (BMD) and bone microstructure parameters.
Results: BMD measurements revealed higher values in specimens after placement in Lugol's solution ($p < 0.05$). Bone microstructure analyses showed increased BV/TV and Tb.Th values in group C ($p < 0.05$). Specimens of group C resulted in clearly decreased Tb.Sp values ($p < 0.05$) in comparison to the control group. Formaldehyde fixation showed minimally altered BMD and bone microstructure measurements without reaching any significance.
Conclusions: MicroCT scans of bone structures are recommended to be conducted natively and immediately after euthanizing rats. MicroCT scans of formaldehyde-fixed specimens must be performed with caution due to a possible slight shift of absolute values of BMD and bone microstructure. Bone analysis of specimens stained by Lugol's solution cannot be recommended.
J Orthop Surg Res 16:254 IF 2.359 (1599)

5.24 Local anisotropy in mineralized fibrocartilage and subchondral bone beneath the tendon-bone interface

The enthesis allows the insertion of tendon into bone thanks to several remarkable strategies. This complex and clinically relevant location often features a thin layer of fibrocartilage sandwiched between tendon and bone to cope with a highly heterogeneous mechanical environment. The main purpose of this study was to investigate whether mineralized fibrocartilage and bone close to the enthesis show distinctive three-dimensional microstructural features, possibly to enable load transfer from tendon to bone. As a model, the Achilles tendon-calcaneus bone system of adult rats was investigated with histology, backscattered electron imaging and micro-computed tomography. The microstructural porosity of bone and mineralized fibrocartilage in different locations including enthesis fibrocartilage, periosteal fibrocartilage and bone away from the enthesis was characterized. We showed that calcaneus bone presents a dedicated protrusion of low porosity where the tendon inserts. A spatially resolved analysis of the trabecular network suggests that such protrusion may promote force flow from the tendon to the plantar ligament, while partially relieving the trabecular bone from such a task. Focusing on the tuberosity, highly specific microstructural aspects were highlighted. Firstly, the interface between mineralized and unmineralized fibrocartilage showed the highest roughness at the tuberosity, possibly to increase failure resistance of a region carrying large stresses. Secondly, fibrochondrocyte lacunae inside mineralized fibrocartilage, in analogy with osteocyte lacunae in bone, had a predominant alignment at the enthesis and a rather random organization away from it. Finally, the network of subchondral channels inside the tuberosity was highly anisotropic when compared to contiguous regions. This dual anisotropy of subchondral channels and cell lacunae at the insertion may reflect the alignment of the underlying collagen network. Our findings suggest that the microstructure of fibrocartilage may be linked with the loading environment. Future studies should characterize those microstructural aspects in aged and or diseased conditions to elucidate the poorly understood role of bone and fibrocartilage in enthesis-related pathologies.
Sci Rep 11:16534 IF 4.379 (1600)

5.25 A novel cryptic splice site mutation in *COL1A2* as a cause of osteogenesis imperfecta

Osteogenesis imperfecta (OI) is an inherited genetic disorder characterized by frequent bone fractures and reduced bone mass. Most cases of OI are caused by dominantly inherited heterozygous mutations in one of the two genes encoding type I collagen, *COL1A1* and *COL1A2*. Here we describe a five-year-old boy with typical clinical, radiological and bone ultrastructural features of OI type I. Establishing the molecular genetic cause of his condition proved difficult since clinical exome and whole exome analysis was repeatedly reported negative. Finally, manual analysis of exome data revealed a silent *COL1A2* variant c.3597 T > A (NM_000089.4), which we demonstrate activates a cryptic splice site. The newly generated splice acceptor in exon 50 is

much more accessible than the wild-type splice-site between the junction of exon 49 and 50, and results in an in-frame deletion of 24 amino acids of the C-terminal propeptide. In vitro collagen expression studies confirmed cellular accumulation and decreased COL1A2 secretion to 45%. This is the first report of a cryptic splice site within the coding region of *COL1A2*. which results in abnormal splicing causing OI. The experience from this case demonstrates that routine diagnostic approaches may miss cryptic splicing mutations in causative genes due to the lack of universally applicable algorithms for splice-site prediction. In exome-negative cases, in-depth analysis of common causative genes should be conducted and trio-exome analysis is recommended.

Bone Rep 15:101110 IF 2.590 (1601)

5.26 New therapeutic options for bone diseases

In recent years, new treatment options for both common and rare bone diseases have become available. The sclerostin antibody romosozumab is the most recently approved drug for the therapy of postmenopausal osteoporosis. Its anabolic capacity makes it a promising treatment option for severe osteoporosis. Other sclerostin antibodies for the treatment of rare bone diseases such as osteogenesis imperfecta are currently being investigated. For rare bone diseases such as X-linked hypophosphatemia (XLH) and hypophosphatasia (HPP), specific therapies are now also available, showing promising data in children and adults with a severe disease course. However, long-term data are needed to assess a sustained benefit for patients.

Wien Med Wochenschr 171:120-5 IF 0.915 (1602)

5.27 The Vienna Bone and Growth Center-care and research in the field of rare diseases

In this special issue of the Wiener Medizinische Wochenschrift (WMW) we present the occasion of the designation of our center of expertise for rare disorders of bone, mineralization, and growth—the Vienna Bone and Growth Center (VBGC)—by the Austrian Federal Ministry of Social Affairs, Health, Care and Consumer Protection in April 2020. In a unique collaboration of four specialized centers in Vienna, a multidisciplinary team within the VBGC cares for patients with these rare disorders from birth to adulthood.

Care for rare disorders has become an important topic within the European Union. European reference networks (ERNs) have been set up with the aim of offering patient care at the highest level in member states. At the same time, ERNs facilitate international expert rounds on individual patients and offer new possibilities in teaching as well as in clinical and basic research. Last but not least, ERNs offer support for patient advocacy groups.

The VBGC is structured paninstitutionally, bringing together multidisciplinary teams consisting of clinicians (pediatric and adult endocrinologists, osteologists, clinical geneticists, pediatric and adult orthopedic surgeons, radiologists), basic scientists and functional therapeutic teams specialized in bone and growth disorders.

Wien Med Wochenschr 171:85 IF 0.915 (1603)

5.28 Bone properties in osteogenesis imperfecta: what can we learn from a bone biopsy beyond histology?

Transiliac bone biopsy samples are used to evaluate histology and bone cell activity in unclear pathological conditions. However, much additional information can be obtained from such bone samples. Using the example of osteogenesis imperfecta (OI), the current article describes how biopsy samples can be further used to study bone material characteristics including the degree of matrix mineralization, organic matrix properties, mineral particle size and bone nanoporosity. OI is a heritable collagen-related disorder that is phenotypically and genetically extremely heterogeneous. One essential finding was that OI bone is hypermineralized independently of clinical severity. Moreover, mineral particles in OI bone are of normal size or even smaller, but more densely packed than normally. Another recent finding was that in some forms of OI, collagen

orientation is highly disorganized, indicating that the collagen-mineral particle network is profoundly altered in OI. These findings have contributed to the understanding of impaired bone strength in OI.

Wien Med Wochenschr 171:111-9 IF 0.915 (1604)

5.29 Six *ALPL* gene variants in five children with hypophosphatasia

Background: Hypophosphatasia (HPP) is a rare hereditary disorder characterized by defective bone and tooth mineralization caused by mutations in the alkaline phosphatase (*ALPL*) gene encoding tissue-nonspecific alkaline phosphatase (TNSALP). Here we performed clinical and molecular studies on 5 HPP children to investigate the pathogenic mechanisms of the *ALPL* gene variants.

Methods: Clinical and genetic analyses were performed on 5 HPP children, and the loci where *ALPL* variants were identified. Plasmids containing the relevant loci were constructed. The molecular and cellular mechanisms of the pathogenic *ALPL* variants were investigated by cellular immunofluorescence, enzyme activity assay, and protein expression assay.

Results: A total of 6 ALPL variants were identified in 5 HPP children: proband 1: c.346G>A (p.A116T); proband 2: c.346G>A (p.A116T)/deletions from c.1097 to c.1099 CCT (p.T366_S367deli) compound heterozygous variant; proband 3: insertion of G from c.1014 to c.1015 (p.H338fs)/c.1446C>A (p.H482Q) compound heterozygous variant; proband 4: c.920C>T (p.P307L); and proband 5: c.883A>G (p.M295V). Twenty-four hours after the HEK-293T was transfected with different variant plasmids, its alkaline phosphatase activity and enzyme protein content were reduced compared with the wild type, and there were differences among different variants. Except for 1014-G-1015+C1446A, the degree of reduction in enzyme activity was negatively correlated with the severity of clinical manifestations. Immunofluorescence revealed that the variants (especially c.883A>G and c.920C>T) caused a decrease in alkaline phosphatase expression in the cellular membrane.

Conclusions: In total, 3 novel variants were identified in these 5 HPP children, the discovery of which will enrich the human *ALPL* gene mutation database. Different variants in the *ALPL* gene can downregulate the activity of TNSALP enzyme (and thus affect its function) by affecting protein expression and translational modifications. The same variant may cause clinical manifestations of different severities in different individuals due to the presence of dominant negative effects, alterations in noncoding sequences, blind area of intron regulatory region sequencing, and variations in environmental and individual factors. The molecular mechanisms via which the *ALPL* gene exerts its expression effect in vivo are highly variable and warrant further investigation.

Ann Transl Med 9:888 IF 3.297 (1605)

5.30 Early postoperative basal insulin therapy versus standard of care for the prevention of diabetes mellitus after kidney transplantation: A multicenter randomized trial

Background: Post-transplantation diabetes mellitus (PTDM) might be preventable.

Methods: This open-label, multicenter randomized trial compared 133 kidney transplant recipients given intermediate-acting insulin isophane for postoperative afternoon glucose ≥140 mg/dl with 130 patients given short-acting insulin for fasting glucose ≥200 mg/dl (control). The primary end point was PTDM (antidiabetic treatment or oral glucose tolerance test-derived 2 hour glucose ≥200 mg/dl) at month 12 post-transplant.

Results: In the intention-to-treat population, PTDM rates at 12 months were 12.2% and 14.7% in treatment versus control groups, respectively (odds ratio [OR], 0.82; 95% confidence interval [95% CI], 0.39 to 1.76) and 13.4% versus 17.4%, respectively, at 24 months (OR, 0.71; 95% CI, 0.34 to 1.49). In the per-protocol population, treatment resulted in reduced odds for PTDM at 12 months (OR, 0.40; 95% CI, 0.16 to 1.01) and 24 months (OR, 0.54; 95% CI, 0.24 to 1.20). After adjustment for polycystic kidney disease, per-protocol ORs for PTDM (treatment versus controls) were 0.21

(95% CI, 0.07 to 0.62) at 12 months and 0.35 (95% CI, 0.14 to 0.87) at 24 months. Significantly more hypoglycemic events (mostly asymptomatic or mildly symptomatic) occurred in the treatment group versus the control group. Within the treatment group, nonadherence to the insulin initiation protocol was associated with significantly higher odds for PTDM at months 12 and 24.
Conclusions: At low overt PTDM incidence, the primary end point in the intention-to-treat population did not differ significantly between treatment and control groups. In the per-protocol analysis, early basal insulin therapy resulted in significantly higher hypoglycemia rates but reduced odds for overt PTDM-a significant reduction after adjustment for baseline differences-suggesting the intervention merits further study.

J Am Soc Nephrol 32:2083-98 IF 10.121 (1606)

5.31 Osteoporosis in pneumological diseases: Joint guideline of the Austrian Society for Bone and Mineral Research (ÖGKM) and the Austrian Society for Pneumology (ÖGP)

Chronic inflammation induces proinflammatory cytokine cascades. In addition to systemic inflammation, hypoxemia, hypercapnia, a catabolic metabolism, gonadal or thyroid dysfunction, musculoskeletal dysfunction and inactivity as well as vitamin D deficiency contribute to an increased risk of fragility fractures. Iatrogenic causes of osteoporosis are long-term use of inhaled or systemic glucocorticoids (GC). Inhalative GC application in asthma is often indicated in childhood and adolescence, but interstitial lung diseases such as chronic organizing pneumonia, COPD, sarcoid or rheumatic diseases with lung involvement are also treated with inhalative or oral GC. In patients with cystic fibrosis, malabsorption in the context of pancreatic insufficiency, hypogonadism and chronic inflammation with increased bone resorption lead to a decrease in bone structure. After lung transplantation, immunosuppression with GC is a risk factor.The underlying pneumological diseases lead to a change in the trabecular and cortical bone microarchitecture and to a reduction in osteological formation and resorption markers. Hypercapnia, acidosis and vitamin D deficiency can accelerate this process and thus increase the individual risk of osteoporotic fragility fractures.A bone mineral density measurement with a T-Score < -2.5 is a threshold value for the diagnosis of osteoporosis; in contrast the vast majority of all osteoporotic fractures occur with a T-Score > -2.5. A history of low-trauma fracture indicates osteological therapy.All antiresorptive or anabolic drugs approved in Austria for the treatment of osteoporosis are also indicated for pneumological patients with an increased fragility fracture risk of bone fractures in accordance with the national reimbursement criteria.

Wien Klin Wochenschr 133 (Suppl 4):155-73 IF 1.704 (1607)

5.32 Age-related alterations and senescence of mesenchymal stromal cells: Implications for regenerative treatments of bones and joints

The most common clinical manifestations of age-related musculoskeletal degeneration are osteoarthritis and osteoporosis, and these represent an enormous burden on modern society. Mesenchymal stromal cells (MSCs) have pivotal roles in musculoskeletal tissue development. In adult organisms, MSCs retain their ability to regenerate tissues following bone fractures, articular cartilage injuries, and other traumatic injuries of connective tissue. However, their remarkable regenerative ability appears to be impaired through aging, and in particular in age-related diseases of bones and joints. Here, we review age-related alterations of MSCs in musculoskeletal tissues, and address the underlying mechanisms of aging and senescence of MSCs. Furthermore, we focus on the properties of MSCs in osteoarthritis and osteoporosis, and how their changes contribute to onset and progression of these disorders. Finally, we consider current treatments that exploit the enormous potential of MSCs for tissue regeneration, as well as for innovative cell-free extracellular-vesicle-based and anti-aging treatment approaches.

Mech Ageing Dev 198:111539 IF 5.432 (1608)

5.33 Clinical course in two children with Juvenile Paget's disease during long-term treatment with intravenous bisphosphonates

Juvenile Paget disease (JPD) is an ultra-rare disease, characterized by loss of function of osteoprotegerin. Osteoprotegerin inhibits osteoclast activation via the receptor activator of nuclear factor κB (RANK) pathway. Severely affected children suffer from bone deformities and pain and require long term anti-resorptive treatment. Due to the rarity of the disease, few long-term follow-up data on the clinical course in children are available. In this report, motor development during infancy and early childhood and the activity of the bone disease based on clinical, radiographic and biochemical parameters are reported in 2 children with severe forms of JPD during long term treatment (4 and 14 years) with bisphosphonates. Results of a bone biopsy in patient 1 after 10 years of treatment and video material of the motor development of patient 2 are provided. Doses per year of pamidronate ranged from 4 to 9 mg/kg bodyweight and were administered in 4-10 courses, yearly. Treatment was adjusted individually according to the presence of bone pain. Motor development was delayed in both children before treatment with bisphosphonates was commenced and improved thereafter. Bone histology revealed a significantly higher heterogeneity of mineralization which was mainly attributed to the increased percentage of low mineralized bone areas. Individualized intravenous treatment with pamidronate resulted in sufficient control of bone pain and suppression of bone turnover with few side effects over the observation period.

Bone Rep 14:100762 IF 2.590 (1609)

5.34 Effect of hormone replacement therapy on bone formation quality and mineralization regulation mechanisms in early postmenopausal women

Post-menopausal osteoporosis is characterized by a negative imbalance between bone formation and bone resorption resulting in a net bone loss, increasing the risk of fracture. One of the earliest interventions to protect against this was hormonal replacement therapy (HRT). Bone strength depends on both the amount and quality of bone, the latter including compositional / material and structural properties. Bone compositional / material properties are greatly dependent on both patient-, and tissue-age. Raman spectroscopy is an analytical tool ideally suited for the determination of bone compositional / material properties as a function of tissue age as it is capable of analyzing areas ~1 × 1 μm2 in tetracycline labeled bone forming areas. Using such analysis of humeri from an ovariectomized primate animal model, we reported that loss of estrogen results in alteration in the mineralization regulation mechanisms by osteoid organic matrix attributes at actively forming bone surfaces. In the present work, we used Raman microspectroscopic techniques to compare osteoid and youngest mineralized tissue composition, as well as relationships between osteoid organic matrix quality and quality attributes of the earliest mineralized tissue in paired iliac crest biopsies obtained from early postmenopausal women before and after two years of HRT therapy. Significant correlations between osteoid proteoglycans, sulfated proteoglycans, pyridinoline, and earliest mineralized tissue mineral content were observed, suggesting that in addition to changes in bone turnover rates, HRT affects the osteoid composition, mineralization regulation mechanisms, and potentially fibrillogenesis.

Bone Rep 14:101055 IF 2.590 (1610)

5.35 Lower limb deformity and gait deviations among adolescents and adults with X-linked hypophosphatemia

Background: X-linked hypophosphatemia (XLH) is a rare genetic disorder characterized by lower limb deformity, gait and joint problems, and pain. Hence, quality of life is substantially impaired. This study aimed to assess lower limb deformity, specific radiographic changes, and gait deviations among adolescents and adults with XLH.

Design: Data on laboratory examination and gait analysis results were analyzed retrospectively. Deformities, osteoarthritis, pseudofractures, and enthesopathies on lower limb radiographs were

investigated. Gait analysis findings were compared between the XLH group and the control group comprising healthy adults.
Patients and controls: Radiographic outcomes were assessed retrospectively in 43 patients with XLH (28 female, 15 male). Gait analysis data was available in 29 patients with confirmed XLH (28 women, 15 men) and compared to a healthy reference cohort (n=76).
Results: Patients with XLH had a lower gait quality compared to healthy controls (Gait deviation index GDI 65.9% +/- 16.2). About 48.3% of the study population presented with a greater lateral trunk lean, commonly referred to as waddling gait. A higher BMI and mechanical axis deviation of the lower limbs were associated with lower gait scores and greater lateral trunk lean. Patients with radiologic signs of enthesopathies had a lower GDI.
Conclusions: This study showed for the first time that lower limb deformity, BMI, and typical features of XLH such as enthesopathies negatively affected gait quality among adolescents and adults with XLH.

Front Endocrinol 12:754084 IF 5.555 (1611)

5.36 Impact of Tenofovir Disoproxil-induced Fanconi Syndrome on bone material quality: A case report

Tenofovir is a nucleotide analog reverse-transcriptase inhibitor (NtARTI) used for treatment of chronic hepatitis B and human immunodeficiency virus (HIV). Fanconi syndrome (FS) is a condition affecting the proximal tubules of the kidney, leading to increased passage and impaired reabsorption of various small molecules such as glucose, phosphate, bicarbonate, and amino acids. Tenofovir disoproxil fumarate (TDF) is one of two pro-drugs of tenofovir associated with a greater nephrotoxicity and renal complications such as FS with subsequent osteomalacia, acute kidney injury, and reduction of glomerular filtration rate (GFR) compared with tenofovir alafenamide (TAF). We present the case of a 33-year-old white woman treated with TDF because of chronic hepatitis B infection suffering four atraumatic fractures over the period of 2 years. The patient was taken off the TDF regimen 3 months before presentation. Initial blood and urine samples suggested the presence of TDF-induced osteomalacia, which was confirmed by transiliac bone biopsy and histomorphometry. Moreover, bone mineral density distribution (BMDD) by quantitative backscattered electron imaging (qBEI) analysis showed that approximately 56% of the bone surface was normally mineralized and 44% showed a reduced mineralization consistent with the presence of osteomalacia. The patient made a significant recovery upon cessation of the causative agent. This case report emphasizes the use of bone biopsy, histomorphometry and qBEI in confirming the diagnosis of drug-induced Fanconi syndrome and associated osteomalacia.

JBMR Plus 5:e10506 (1612)

5.37 Clinical phenotype and bone biopsy characteristics in a child with Proteus syndrome

Proteus syndrome is a rare genetic disorder, which is characterized by progressive, segmental, or patchy overgrowth of diverse tissues of all germ layers, including the skeleton. Here, we present a 9-year-old girl with a somatic-activating mutation (c.49G > A; p.Glu17Lys) in AKT1 gene in a mosaic status typical for Proteus syndrome. She presented with hemihypertrophy of the right lower limb and a "moccasin" lesion among others. A transiliac bone biopsy was analyzed for bone histology/histomorphometry as well as bone mineralization density distribution (BMDD) and osteocyte lacunae sections (OLS) characteristics based on quantitative backscattered electron imaging. Bone histomorphometry revealed highly increased mineralizing surface (Z-score + 2.3) and mineral apposition rate (Z-score + 19.3), no osteoclasts (Z-score - 2.1), and an increased amount of primary bone in the external cortex. BMDD abnormalities included a decreased mode calcium concentration in cancellous bone (Z-score - 1.7) and an increased percentage of highly mineralized cortical bone area (Z-score + 2.4) compared to reference. OLS characteristics showed several differences compared to reference data; among them, there were the highly increased

OLS-porosity, OLS-area, and OLS-perimeter on the external cortex (Z-scores + 6.8, + 4.4 and 5.4, respectively). Our findings suggest that increased bone formation reduced matrix mineralization in cancellous bone while the enhanced amount of primary bone in the external cortex increased the portion of highly mineralized cortical bone and caused OLS-characteristics abnormalities. Our results indicate further that remodeling of primary bone might be disturbed or delayed in agreement with the decreased number of osteoclasts observed in this child with Proteus syndrome.

Calcif Tissue Int 109:586-95 IF 4.333 (1613)

5.38 Fourier-Transform Infrared Spectroscopy of epiretinal membranes and internal limiting membranes after pars plana vitrectomy with membrane peeling

Introduction: Fourier-transform infrared imaging (FTIRI) enables examination of protein secondary structure in the analyzed tissues. Aim of our study was to examine the distribution of secondary structures in epiretinal membranes and internal limiting membranes, and to explore possible associations to other diagnostic variables. Methods: This prospective pilot study included patients scheduled for pars plana vitrectomy with membrane peeling. Epiretinal membranes and internal limiting membranes were harvested during surgery and placed on a BaF2window for postsurgical FTIRI analysis. Infrared hyperspectral images were subjected to second and fourth derivative analysis, to obtain information of the protein secondary structures present in the tissues. Results: Samples of 43 patients were analysed, with the triple helical domain showing the highest prevalence in the examined tissues. The other secondary structures (beta sheet, random coil, beta turn) showed a heterogenous distribution in the examined samples, without specific associations to indication of surgery, comorbidities, outcomes from optical coherence tomography, and intrasurgical findings. Conclusions: Fourier-transform infrared imaging enables analysis of the spatial distribution of protein secondary structures in the examined tissues, thus is a useful analytical technique for the analysis of epiretinal membranes and internal limiting membranes.

Ophthalmic Res 64:793-7 IF 2.892 (1614)

5.39 Abnormal bone tissue organization and osteocyte lacunocanalicular network in early-onset osteoporosis due to *SGMS2* mutations

Pathological variants in *SGMS2*, encoding sphingomyelin synthase 2 (SMS2), result in a rare autosomal dominant skeletal disorder with cranial doughnut lesions. The disease manifests as early-onset osteoporosis or a more severe skeletal dysplasia with low bone mineral density, frequent fractures, long-bone deformities, and multiple sclerotic cranial lesions. The exact underlying molecular features and skeletal consequences, however, remain elusive. This study investigated bone tissue characteristics in two adult males with a heterozygous *SGMS2* mutation p.Arg50* and significant bone fragility. Transiliac bone biopsy samples from both (patient 1: 61 years; patient 2: 29 years) were analyzed by bone histomorphometry, confocal laser scanning microscopy, and quantitative backscattered electron imaging (qBEI). Bone histomorphometry portrayed largely normal values for structural and turnover parameters, but in both patient 1 and patient 2, respectively, osteoid thickness (−1.80 SD, −1.37 SD) and mineralizing surface (−1.03 SD, −2.73 SD) were reduced and osteoid surface increased (+9.03 SD, +0.98 SD), leading to elevated mineralization lag time (+8.16 SD, +4.10 SD). qBEI showed low and heterogeneous matrix mineralization (CaPeak −2.41 SD, −3.72 SD; CaWidth +7.47 SD, +4.41 SD) with a chaotic arrangement of collagenous fibrils under polarized light. Last, osteocyte lacunae appeared abnormally large and round in shape and the canalicular network severely disturbed with short-spanned canaliculi lacking any orderliness or continuity. Taken together, these data underline a central role for functional SMS2 in bone matrix organization and mineralization, lacunocanalicular network, and in maintaining skeletal strength and integrity. These data bring new knowledge on changes in bone histology resulting from abnormal sphingomyelin metabolism and aid en route to better understanding of sphingolipid-related skeletal disorders.

6 Aktivitäten in Wissenschafts-Organisation und Administration

6.1 Kongressorganisation,Tagungsleitungen und Fortbildung

6.1.1 Fortbildung

Martina Behanova absolvierte den online Kurs „Statistical Analysis with R for Public Health“.

6.1.2 Kongressorganisation

Das gemeinsame Retreat von LBIO und MPI fand nach der Zwangspause im Jahr 2020 wieder von 21.-23. Oktober in Illmitz/Bgld statt.

Roland Kocijan hatte sowohl beim IOF Congress, 26 – 28 August als auch beim ECTS Clinical Training Course on Metabolic Bone Diseases, 2 – 3 September einen Vorsitz inne, Jochen Zwerina bei der ÖGR Jahrestagung, 25. – 27. November.

6.2 Aktivitäten in nationalen und internationalen wissenschaftlichen Gesellschaften

Jochen Zwerina und Judith Haschka sind Vorstandsmitglieder der Österreichischen Gesellschaft für Knochen und Mineralstoffwechsel (ÖGKM) und Mitglieder der Österreichischen Gesellschaft für Rheumatologie & Rehabilitation (ÖGR).

Roland Kocijan und Nadja Fratzl-Zelman sind Mitglieder des Wissenschaftlichen Beirates der Österreichischen Gesellschaft für Knochen und Mineralstoffwechsel (ÖGKM).

Roland Kocijan ist außerdem Mitglied der HPP International Working Group.

Markus Hartmann ist sowohl Mitglied der Österreichischen (ÖPG) als auch der Amerikanischen (APS) Physikalischen Gesellschaft.

Martina Behanova ist Mitglied der Österreichischen Gesellschaft für Public Health (ÖGPH) und der Slovak Public Health Association (SAVEZ), der Österreichischen Gesellschaft für Knochen und Mineralstoffwechsel (ÖGKM) und der European Calcified Tissue Society (ECTS).

Sonja Jäger ist Mitglied der European Calcified Tissue Society (ECTS), der American Society for Bone and Mineral Research (ASBMR), der Bone Research Society (BRS), Österreichischen Physikalischen Gesellschaft (ÖPG), der International Society of Bone Morphometrie (ISBM), der Society for Applied Spectroscopy, der Vibrational Coblentz Society und der ECTS Website & Social Media Action Group.

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

6.3 Tagungsaktivitäten

Die MitarbeiterInnen des Instituts nahmen an zahlreichen nationalen und internationalen wissenschaftlichen Tagungen teil, wie zum Beispiel: Annual European Calcified Tissue Society (ECTS) Congress, Annual Meeting of the American Society for Bone and Mineral Research (ASMBR), European League Against Rheumatism (EULAR) oder European Meeting on Intermediate Filaments – auch wenn viele dieser Tagungen 2021 virtuell abgehalten wurden.

Details unter 7.1.2 Abstracts (1618 – 1637) und 7.1.3 Invited talks (V596 – V603).

6.4 Lehrtätigkeit

Jochen Zwerina bot die Vorlesungen „Osteoimmunologie: Experimentelle und klinische Aspekte“ (2 SSt) und „Vaskulitis“ (2 SSt) an der Universität Erlangen an und war Vortragender bei der Hauptvorlesung „Rheumatologie“.

Markus Hartmann hielt im WS 2020/21 Vorlesung und Übungen für Werkstoffmodellierung auf atomarer Ebene an der Montanuniverstät Leoben (jeweils 2 SSt., gemeinsam mit David Holec).

Stéphane Blouin und Barbara Misof hielten jeweils im WS 2020/2021 und im SS 2021 gemeinsam den Distant Learning Journal Club (Seminar) „Orthopädie und Unfallchirurgie“ (je 1 SSt) an der Medizinischen Universität Wien.

Nadja Fratzl-Zelman hielt jeweils im WS 2020/2021 und im SS 2021 einen Distance Learning Journal Club (Seminar) „Bones and Joint Regeneration“ (2 SSt) und im WS 2020/2021 eine Basic Lecture über Osteogenesis Imperfecta (2 SSt) an der Medizinischen Universität Wien.

Roland Kocijan hielt an der Sigmund Freud Universität Wien die Vorlesungen „Osteologie“ (0,5 SSt), „Osteoporose & Osteomalazie“ (0,5 SSt), „Seltene Knochenerkrankungen“ (0,5 SSt) sowie einen Journal Club (1 SSt).

An der Medizinischen Universität Wien war er Co-Vorsitzender bei der Diplomprüfung „Cross-sectional Evaluation of Quality of Life in Patients with X- Linked Hypophosphatemic Rickets”.

Darüber hinaus betreute Roland Kocijan fünf Diplomarbeiten: Amadea Medibach (Complementary & Alternative Medicine in Bone Diseases), SFU; Michaela Layr (MIO-BX Study: Bone biopsy in male idiopathic osteoporosis: a retrospective analysis), Theresa Stockinger (COVID-BONE: Osteoporosis in the era of COVID, Carina Damberger (Wie präzise ist die Verwendung eines 3D Planungsprogramms und patientenspezifischer Instrumente bei inversen Schulter-Totalendoprothesen?) und Lisa Bachfischer (Enthesiopathy in XLH: a sonography study).

Judith Haschka hielt sowohl im WS 2020/2021 sowie im SS 2021 einen Journalclub (Seminar) für „Bones and Joint Regeneration“ (1 SSt) an der Medizinischen Universität Wien.

Thomas Dechat hielt im Rahmen des Masterstudiums „Molecular Biotechnologies“ am FH-Campus Wien im Sommersemester 2021 einen Stammzellenkurs (3 SSt).

Er betreute zwei Masterstudentinnen (Studium Molekulare Biologie) der Universität Wien (Johanna Besold, Claudia Hufnagel), eine Masterstudentin (Genetik & Entwicklungsbiologie) der Universität Wien im Rahmen eines FemTech-Praktikums (Lejla Mastalic), eine Bachelorstudentin (Biomedizinische Analytik) der FH Wiener Neustadt (Sandra Wagner) und einen Bachelorstudenten (Biomedizin und Biotechnologie) der Veterinärmedizinischen Universität Wien im Rahmen eines 3-monatigen Pflichtpraktikums (Lukas Rath).

Ruth Fritsch-Stork hielt im Sommersemester 2021 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 2021/2022 dasselbe Programm plus eine Anamnese Blockvorlesung und Klinische Fallbesprechung für den Masterstudiengang (insgesamt jeweils 3 SSt).

Ruth Fritsch-Stork hält den Lehrstuhl für Rheumatologie an der Sigmund Freud Privatuniversität Wien.

6.5 Reviewertätigkeit

Jochen Zwerina ist Mitglied des Editorial Board des Journals für Kochen- und Mineralstoffwechsel. Darüber hinaus nahm er am Review-Prozess der Abstracts für die ECTS 2021 teil.

Barbara Misof war Abstract-Begutachterin für das ECTS-Meeting 2021. Sie war außerdem Reviewerin für die Zeitschriften Calcified Tissue International,Bone und Renal Failure.

Markus Hartmann war Gutachter für das National Science Center Polen, sowie für die Zeitschrift Nutrients.

Nadja Fratzl-Zelman war Gutachterin für die Zeitschriften Journal of Structural Biology und Scientific Reports sowie für den Dutch Research Council (NWO)

Stéphane Blouin war Reviewer für die Zeitschriften Calcified Tissue International, Frontier in Endocrinology and Scientific Report

Martina Behanova erstellte Reviwes für Journal of Clinical Medicine, Therapeutic Advances in Gastroenterology, BMC Musculoskeletal disorders, Journal of International Medical Research. Außerdem ist sie Mitglied des Editorial Board des International Journal of Public Health.

Roland Kocijan war Begutachter für mehrere internationale Journale sowie für einen Antrag an den Medizinisch-wissenschaftlicher Fonds des Bürgermeisters der Bundeshauptstadt Wien.

Thomas Dechat ist Academic Collection Editor für die Topical Collection "Lamins and Laminopathies" und Guest Editor für das Special Issue "The New Frontier of Therapies for Nuclear Envelope and Lamin-Related Diseases: Selected Papers from 2019 International Meeting on Laminopathies" bei Cells. Er verfasste Peer reviews für die Journale Cells und Toxins.

Eleftherios Paschalis ist Associate Editor des Journal of Musculoskeletal and Neuronal Interactions (JMNI), Editorial Board Member von Calcified Tissue International, Bone und F1000 Medicine. Er erstellte Reviews für: Journal of Bone & Mineral Research (JBMR), American Society of Bone & Mineral Research (ASBMR), Acta Biomaterialia, National Institutes of Health (NIH), European Calcified Tissue Society (ECTS), Journal of Biomedical Optics, Osteoporosis International, PLoS One, Nature Scientific Reports, Journal of Structural Biology, Applied Spectroscopy, Amgen Bone Biology Fellowship, Annals of the New York Academy of Sciences, Journal of Orthopaedic Research, Osteoarthritis and Cartilage, European Cells & Materials, Journal of Spectroscopy, Journal of the Mechanical Behavior of Biomedical Materials, Journal of Biophotonics, Clinical Orthopaedics and Related Research und Journal of Raman Spectroscopy.

Sonja Jäger erstellte Reviews für Calcified Tissue International, Journal of Orthopaedic Research, Cells, Diagnostics, Molecules, Sensors und JBMR.

6.6 Beteiligung an Projekten

- Untersuchung von klinischen, serologischen und genetischen Faktoren der lgG4 – Related Disease
  Medizinisch-Wissenschaftlicher Fonds des Bürgermeisters der Bundeshauptstadt Wien, 15069
  Projektleitung: Jochen Zwerina
  01.08.2015 – 31.12.2021
- Lamins in Bone
  FFG (FemTech) 881845
  Projektleitung: Thomas Dechat
  08.02.2021 – 07.08.2021
- Occult Bone Disease in Sudden Childhood Death: a Post-Mortem Study
  Kooperation mit Birmingham Women’s & Children’s NHS Foundation Trust
  Projektleitung: Wolfgang Högler
  Projektkoordination LBIO: Nadja Fratzl-Zelman
  01.01.2018 – 31.12.2022
- Bone material properties in transiliac bone biopsies in adult patients with X-linked Hypophosphatemia (XLH) before and after a 48-week treatment with Burosumab
  Kooperation mit Ultragenyx
  Projektkoordination LBIO: Nadja Fratzl-Zelman

01.09.2019 - 30.04.2021

- Identification and Molecular Genetic Screening of Patients with Hypophosphatasis
  Klinische Studie an der 1. Medizinischen Abteilung im Hanusch-KH
  Projektleitung: Roland Kocijan
  01.08.2019 – 31.07.2022

6.7 Preise und Nominierungen

Daniel Arian Kraus erhielt den Young Investigator Award der österreichischen Gesellschaft für Knochen und Mineralstoffwechsel für seinen Beitrag „Analysis of bone architecture using fractal-based TX-Analyzer™ in adult patients with osteogenesis imperfecta".

6.8 Personelle Daten

6.8.1 Neueintritte

Johanna Besold, MSc., die bereits im Rahmen ihres Masterstudiums am LBIO tätig war, wurde mit März als Laborfachkraft angestellt.

Lejla Mastalic, BSc. trat im Februar ihr zweites sechsmonatiges FemTech Praktikum am LBIO an. Im Anschluss wurde sie für ein weiteres halbes Jahr angestellt, um ihr die Fertigstellung ihrer Masterarbeit zu ermöglichen.

Für den Zeitraum, in dem Johanna Besold, MSc in Bildungskarenz ist (11.9.2021-31.3.2022), wurde Claudia Hufnagel, BSc. angestellt, die bereits seit Oktober 2019 im Rahmen eines Studiumabschluss-Stipendiums ihre Masterarbeit am LBIO erstellt.

Mit Oktober verstärkte die PhD-Studentin Chloe Jones, MSc. das LBIO Team im UKH Meidling. Sie konnte die Ausschreibung dieser Position im Rahmen des Forschungsprojektes „OLCN in bone during ageing" für sich entscheiden.

6.8.2 Austritte

Ghazal Hedjazi, MSc., die am LBIO ihre PhD-Arbeit verfasst hat, verließ das Institut mit Ende Oktober.

6.8.3 Diverses

Johanna Besold, MSc nimmt vom 11.9.2021 bis 31.3.2022 eine Bildungskarenz in Anspruch, um in Frankreich am Institute for Research on Cancer and Aging of Nice (IRCAN) ein Praktikum zu absolvieren.

Claudia Hufnagel, BSc, eine Masterstudentin der Molekularen Biologie, arbeitete weiterhin im Rahmen eines Studiumabschluss-Stipendiums an ihrer Masterarbeit.

Sandra Wagner, eine Studentin der FH Wiener Neustadt (Biomedizinische Analytik) erstellte von Februar bis April ihre Bachelorarbeit am LBIO.

Der Bachelorstudent Lukas Rath der Veterinärmedizinischen Universität Wien (Biomedizin und Biotechnologie) absolvierte von Juli bis September ein Pflichtpraktikum am LBIO.

Im Oktober war die PhD Studentin Alexandra Tits, BSc. der Universität Liège für einen Forschungsaufenthalt am LBIO.

Dr. Saila Marita Laakso aus dem Team von Prof. Outi Mäkitie an der Universität Helsinki verbrachte im November einen Forschungsmonat am LBIO.

7 Publications and oral presentations

7.1 Publications of the year 2021

7.1.1 Original papers

1577. Fratzl-Zelman N, Wesseling-Perry K, Mäkitie RE, Blouin S, Hartmann MA, Zwerina J, Välimäki VV, Laine CM, Välimäki MJ, Pereira RC, Mäkitie O 2021 Bone material properties and response to teriparatide in osteoporosis due to WNT1 and PLS3 mutations. Bone 146:115900
IF 4.398

1578. Müller MM, Schwaiger E, Kurnikowski A, Haidinger M, Ristl R, Tura A, Pacini G, Werzowa J, Hecking M 2021 Glucose metabolism after kidney transplantation: Insulin release and sensitivity with tacrolimus- versus belatacept-based immunosuppression. Am J Kidney Dis 77:462-4
IF 8.860

1579. Grillari J, Mäkitie RE, Kocijan R, Haschka J, Carro Vazquez D, Semmelrock E, Hackl M 2021 Circulating miRNAs in bone health and disease. Bone 145:115787
IF 4.398

1580. Buch S, Sharma A, Ryan E, Datz C, Griffiths WJH, Way M, Buckley TWM, Ryan JD, Stewart S, Wright C, Dongiovanni P, Fracanzani A, Zwerina J, Merle U, Weiss KH, Aigner E, Krones E, Dejaco C, Fischer J, Berg T, Valenti L, Zoller H, McQuillin A, Hampe J, Stickel F, Morgan MY 2021 Variants in PCSK7, PNPLA3 and TM6SF2 are risk factors for the development of cirrhosis in hereditary haemochromatosis. Aliment Pharmacol Ther 53:830-43
IF 8.171

1581. Wienke J, Mertens JS, Garcia S, Lim J, Wijngaarde CA, Yeo JG, Meyer A, van den Hoogen LL, Tekstra J, Hoogendijk JE, Otten HG, Fritsch-Stork RDE, de Jager W, Seyger MMB, Thurlings RM, de Jong EMGJ, van der Kooi AJ, van der Pol WL; Dutch Juvenile Myositis Consortium, Arkachaisri T, Radstake TRDJ, van Royen-Kerkhof A, van Wijk F 2021 Biomarker profiles of endothelial activation and dysfunction in rare systemic autoimmune diseases: implications for cardiovascular risk. Rheumatology (Oxford) 60:785-801
IF 7.580

1582. Kocijan R, Behanova M, Reichardt B, Haschka J, Kocijan A, Zwerina J 2021 Poor adherence to parenteral osteoporosis therapies during COVID-19 pandemic. Arch Osteoporos 16:46
IF 2.617

1583. Gamsjaeger S, Fratzl P, Paschalis EP 2021 Interplay between mineral crystallinity and mineral accumulation in health and postmenopausal osteoporosis. Acta Biomater 124:374-81
IF 8.947

1584. Paschalis EP, Dempster DW, Gamsjaeger S, Rokidi S, Hassler N, Brozek W, Chan-Diehl FW, Klaushofer K, Taylor KA 2021 Mineral and organic matrix composition at bone forming surfaces in postmenopausal women with osteoporosis treated with either teriparatide or zoledronic acid. Bone 145:115848
IF 4.398

1585. Kirchler C, Husar-Memmer E, Rappersberger K, Thaler K, Fritsch-Stork R 2021 Type I Interferon as cardiovascular risk factor in systemic and cutaneous lupus erythematosus: A systematic review. Autoimmun Rev 17:102794

IF 9.754

1586. Amuno S, Shekh K, Kodzhahinchev V, Niyogi S, Al Kaissi A 2021 Skeletal pathology and bone mineral density changes in wild muskrats (Ondatra zibethicus) and red squirrels (Tamiasciurus hudsonicus) inhabiting arsenic polluted areas of Yellowknife, Northwest Territories (Canada): A radiographic densitometry study. Ecotoxicol Environ Saf 208:111721
IF 6.291

1587. Alccayhuaman KAA, Tangl S, Blouin S, Hartmann MA, Heimel P, Kuchler U, Lee JS, Gruber R 2021 Osteoconductive properties of a volume-stable collagen matrix in rat calvaria defects: A pilot study. Biomedicines 9:732
IF 6.081

1588. Naetar N, Georgiou K, Knapp C, Bronshtein I, Zier E, Fichtinger P, Dechat T, Garini Y, Foisner R 2021 LAP2alpha maintains a mobile and low assembly state of A-type lamins in the nuclear interior. eLife 10:e63476
IF 7.080

1589. Tang CC, Castro Andrade CD, O'Meara MJ, Yoon SH, Sato T, Brooks DJ, Bouxsein ML, da Silva Martins J, Wang J, Gray NS, Misof B, Roschger P, Blouin S, Klaushofer K, Velduis-Vlug A, Vegting Y, Rosen CJ, O'Connell D, Sundberg TB, Xavier RJ, Ung P, Schlessinger A, Kronenberg HM, Berdeaux R, Foretz M, Wein MN 2021 Dual targeting of salt inducible kinases and CSF1R uncouples bone formation and bone resorption. eLife 10:e67772
IF 7.080

1590. Kronschläger M, Ruiß M, Dechat T, Findl O 2021 Single high-dose peroral caffeine intake inhibits ultraviolet radiation-induced apoptosis in human lens epithelial cells in vitro. Acta Ophthalmol 99:e587-93
IF 3.761

1591. Groot N, Kardolus A, Bijl M, Dolhain R, Teng O, Zirkzee E, de Leeuw K, Fritsch-Stork R, Burdorf L, Bultink I, Kamphuis S 2021 Effects of childhood-onset SLE on academic achievements and employment in adult life. J Rheumatol 48:915-23
IF 3.350

1592. Weigl M, Kocijan R, Ferguson J, Leinfellner G, Heimel P, Feichtinger X, Pietschmann P, Grillari J, Zwerina J, Redl H, Hackl M 2021 Longitudinal changes of circulating miRNAs during bisphosphonate and teriparatide treatment in an animal model of postmenopausal osteoporosis. J Bone Miner Res 36:1131-44
IF 6.741

1593. Schanda JE, Huber S, Behanova M, Haschka J, Kraus DA, Meier P, Bahrami A, Zandieh S, Muschitz C, Resch H, Mähr M, Rötzer K, Uyanik G, Zwerina J, Kocijan R 2021 Analysis of bone architecture using fractal-based TX-Analyzer™ in adult patients with osteogenesis imperfecta. Bone 147:115915
IF 4.398

1594. Behanova M, Haschka J, Zwerina J, Wascher TC, Reichardt B, Klaushofer K, Kocijan R 2021 The doubled burden of diabetic bone disease: hip fracture and post-hip fracture mortality. Eur J Endocrinol 184:627-36
IF 6.664

1595. Kuroda Y, Kawaai K, Hatano N, Wu Y, Takano H, Momose A, Ishimoto T, Nakano T, Roschger P, Blouin S, Matsuo K 2021 Hypermineralization of hearing-related bones by a specific osteoblast subtype. J Bone Miner Res 36:1535-47
IF 6.741

1596. Mähr M, Blouin S, Behanova M, Misof BM, Glorieux FH, Zwerina J, Rauch F, Hartmann MA, Fratzl-Zelman N 2021 Increased osteocyte lacunae density in the hypermineralized bone matrix of children with osteogenesis imperfecta type I. Int J Mol Sci 22:4508
IF 5.923

1597. Hartmann MA, Blouin S, Misof BM, Fratzl-Zelman N, Roschger P, Berzlanovich A, Gruber GM, Brugger PC, Zwerina J, Fratzl P 2021 Quantitative backscattered electron imaging of bone using a thermionic or a field emission electron source. Calcif Tissue Int 109:190-202
IF 4.333

1598. Ayoubi M, van Tol AF, Weinkamer R, Roschger P, Brugger PC, Berzlanovich A, Bertinetti L, Roschger A, Fratzl P 2021 3D interrelationship between osteocyte network and forming mineral during human bone remodeling. Adv Healthcare Mater 10:e2100113
IF 9.933

1599. Feichtinger X, Heimel P, Keibl C, Hercher D, Schanda JE, Kocijan R, Redl H, Grillari J, Fialka C, Mittermayr R 2021 Lugol's solution but not formaldehyde affects bone microstructure and bone mineral density parameters at the insertion site of the rotator cuff in rats. J Orthop Surg Res 16:254
IF 2.359

1600. Tits A, Plougonven E, Blouin S, Hartmann MA, Kaux JF, Drion P, Fernandez J, van Lenthe GH, Ruffoni D 2021 Local anisotropy in mineralized fibrocartilage and subchondral bone beneath the tendon-bone interface. Sci Rep 11:16534
IF 4.379

1601. El-Gazzar A, Mayr JA, Voraberger B, Brugger K, Blouin S, Tischlinger K, Duba HC, Prokisch H, Fratzl-Zelman N, Högler W 2021 A novel cryptic splice site mutation in *COL1A2* as a cause of osteogenesis imperfecta. Bone Rep 15:101110
IF 2.590

1602. Kocijan R, Haschka J, Feurstein J, Zwerina J 2021 New therapeutic options for bone diseases. Wien Med Wochenschr 171:120-5
IF 0.915

1603. Haeusler G, Ganger R, Kocijan R, Fratzl-Zelman N 2021 The Vienna Bone and Growth Center-care and research in the field of rare diseases. Wien Med Wochenschr 171:85
IF 0.915

1604. Mähr M, Blouin S, Misof BM, Paschalis EP, Hartmann MA, Zwerina J, Fratzl-Zelman N 2021 Bone properties in osteogenesis imperfecta: what can we learn from a bone biopsy beyond histology? Wien Med Wochenschr 171:111-9
IF 0.915

1605. Su N, Zhu M, Cheng X, Xu K, Kocijan R, Zhang H 2021 Six *ALPL* gene variants in five children with hypophosphatasia. Ann Transl Med 9:888
IF 3.297

1606. Schwaiger E, Krenn S, Kurnikowski A, Bergfeld L, Pérez-Sáez MJ, Frey A, Topitz D, Bergmann M, Hödlmoser S, Bachmann F, Halleck F, Kron S, Hafner-Giessauf H, Eller K, Rosenkranz AR, Crespo M, Faura A, Tura A, Song PXK, Port FK, Pascual J, Budde K, Ristl R, Werzowa J, Hecking M 2021 Early postoperative basal insulin therapy versus standard of care for the prevention of diabetes mellitus after kidney transplantation: A multicenter randomized trial. J Am Soc Nephrol 32:2083-98
IF 10.121

1607. Muschitz C, Zwick RH, Haschka J, Dimai HP, Rauner M, Amrein K, Wakolbinger R, Jaksch P, Eber E, Pietschmann P 2021 Osteoporose bei pneumologischen Erkrankungen.

Gemeinsame Leitlinie der Österreichischen Gesellschaft für Knochen und Mineralstoffwechsel (ÖGKM) und der Österreichischen Gesellschaft für Pneumologie (ÖGP). Wien Klin Wochenschr 133 (Suppl 4):155-73
IF 1.704

1608. Zupan J, Strazar K, Kocijan R, Nau T, Grillari J, Marolt Presen D 2021 Age-related alterations and senescence of mesenchymal stromal cells: Implications for regenerative treatments of bones and joints. Mech Ageing Dev 198:111539
IF 5.432

1609. Höppner J, Steff K, Misof BM, Schündeln MM, Hövel M, Lücke T, Grasemann C 2021 Clinical course in two children with Juvenile Paget's disease during long-term treatment with intravenous bisphosphonates. Bone Rep 14:100762
IF 2.590

1610. Gamsjaeger S, Eriksen EF, Paschalis EP 2021 Effect of hormone replacement therapy on bone formation quality and mineralization regulation mechanisms in early postmenopausal women. Bone Rep 14:101055
IF 2.590

1611. Mindler GT, Kranzl A, Stauffer A, Kocijan R, Ganger R, Radler C, Haeusler G, Raimann A 2021 Lower limb deformity and gait deviations among adolescents and adults with X-linked hypophosphatemia. Front Endocrinol 12:754084
IF 5.555

1612. Hadzimuratovic B, Haschka J, Hartmann MA, Blouin S, Fratzl-Zelman N, Zwerina J, Kocijan R 2021 Impact of Tenofovir Disoproxil-induced Fanconi Syndrome on bone material quality: A case report. JBMR Plus 5:e10506

1613. Al Kaissi A, Misof BM, Laccone F, Blouin S, Roschger P, Kircher SG, Shboul M, Mindler GT, Girsch W, Ganger R 2021 Clinical phenotype and bone biopsy characteristics in a child with Proteus syndrome. Calcif Tissue Int 109:586-95
IF 4.333

1614. Leisser C, Paschalis E, Rokidi S, Behanova M, Ruiss M, Burgmüller W, Findl O 2021 Fourier-Transform Infrared Spectroscopy of epiretinal membranes and internal limiting membranes after pars plana vitrectomy with membrane peeling. Ophthalmic Res 64:793-7
IF 2.892

1615. Mäkitie RE, Blouin S, Välimäki VV, Pihlström S, Määttä K, Pekkinen M, Fratzl-Zelman N, Mäkitie O, Hartmann MA 2021 Abnormal bone tissue organization and osteocyte lacunocanalicular network in early-onset osteoporosis due to *SGMS2* mutations. JBMR Plus 5:e10537

1616. Besold JM 2021 The role of a microtubule-associated motor protein in healthy and diseased bone development. Masterarbeit

1617. Wagner S 2021 Nukleäre Lamine in unbehandelten und mit Statinen und Bisphosphonaten behandelten Knochenzellen. Bachelorarbeit

Publications in print

Feichtinger X, Heimel P, Tangl S, Keibl C, Nürnberger S, Schanda JE, Hercher D, Kocijan R, Redl H, Grillari J, Fialka C, Mittermayr R 2022 Improved biomechanics in experimental chronic rotator cuff repair after shockwaves is not reflected by bone microarchitecture. PLoS One 17:e0262294
IF 3.240

Hadzimuratovic B, Mittelbach A, Bahrami A, Zwerina J, Kocijan R 2020 Confluent abscesses in autochthonous back muscles after spinal injections: A case report and narrative review of the literature on low back pain and spinal injections. Wien Med Wochenschr Aug 3. doi: 10.1007/s10354-020-00773-y. Online ahead of print
IF 0.915

Al Kaissi A, Ryabykh S, Ochirova P, Bouchoucha S, Kenis V, Shboul M, Ganger R, Grill F, Kircher SG 2020 Arthrogryposis is a descriptive term, not a specific disease entity: Escobar syndrome is an example. Minerva Pediatr Jun 12. doi: 10.23736/S0026-4946.20.05796-5. Online ahead of print
IF 1.312

Al Kaissi A, Ryabykh S, Ochirova P, Kareem AA, Kenis V, Ganger R, Grill F, Kircher GS 2020 The articular and the craniocervical abnormalities are of confusing age of onset in patients with Maroteaux-Lamy disease (MPS VI). Minerva Pediatr Aug 4. doi: 10.23736/S0026-4946.20.05645-5. Online ahead of print
IF 1.312

Vaglio A, Maritati F, Zwerina J 2020 Response to: 'Eosinophilic granulomatosis with polyangiitis can manifest lacrimal and salivary glands swelling by granulomatous inflammation: a potential mimicker of IgG4-related disease' by Akiyama et al. Ann Rheum Dis Jun 26;annrheumdis-2020-218174. doi: 10.1136/annrheumdis-2020-218174. Online ahead of print
IF 19.103

7.1.2 Abstracts

1618. Gamsjaeger S, Eriksen E, Paschalis EP 2021 Effect of hormone replacement therapy on bone formation quality and mineralization regulation mechanisms in early postmenopausal women. ECTS, May 6 – 8, Digital Congress, abstract P159 and oral poster presentation

1619. Hedjazi G, Guterman-Ram G, Blouin S, Hartmann MA, Schemenz V, Wagermaier W, Fratzl P, Zwerina J, Fratzl-Zelman N, Marini JC 2021 Novel murine model of atypical type VI osteogenesis imperfecta has altered osteocyte canalicular network, disordered collagen orientation along with hypermineralization of bone matrix. ECTS, May 6 – 8, Digital Congress, abstract COP23 and oral presentation

1620. Liu Y, Hefferan T, Fratzl-Zelman N, Marini J 2021 Bone cell functions in PPIB knock-out mouse model for type IX osteogenesis imperfecta are distinct from classical dominant OI. ECTS, May 6 – 8, Digital Congress, abstract P196 and poster presentation

1621. Feurstein J, Behanova M, Haschka J, Roetzer K, Uyanik G, Witsch-Baumgartner M, Schett G, Zwerina J, Kocijan R 2021 Identifying adult hypophosphatasis in the rheumatology unit. EULAR, June 2 – 5, Virtual Congress, abstract POS1137 and poster presentation

1622. Hedjazi G, Guterman-Ram G, Blouin S, Hartmann MA, Schemenz V, Wagermaier W, Fratzl P, Zwerina J, Fratzl-Zelman N, Marini JC 2021 Novel murine model of atypical type VI osteogenesis imperfecta has altered matrix mineralization, osteocyte canalicular network and disordered collagen orientation. The Young Scientist Association, June 17 – 18, Virtual Event, abstract and poster presentation

1623. Tits A, Blouin S, Kaux JF, Drion P, van Lenthe GH, Weinkamer R, Hartmann MA, Ruffoni D 2021 Microstructural anisotropy and material gradients in mineralized fibrocartilage at the tendon-bone insertion. 26th Congress of the European Society of Biomechanics (ESB 2021), July 11 – 14, Online Event, abstract 1390 and oral presentation

1624. Hufnagel C, Simon C, Spitzer S, Hassler N, Zwerina J, Dechat T 2021 The role of A-type lamins in bone development. European Meeting on Intermediate Filaments, September 5 - 8, Rolduc, Netherlands, abstract S03 and oral presentation

1625. Besold J, Hufnagel C, Simon C, Spitzer S, Hassler N, Zwerina J, Dechat T 2021 Vimentin in wild type and mutant bone precursor-cells. European Meeting on Intermediate Filaments, September 5 – 8, Rolduc, Netherlands, abstract F03 and poster presentation

1626. Paschalis EP, Gamsjaeger S, Klaushofer K, Shane E, Cohen A, Stepan J, Pavo I, Eriksen EF, Taylor KA, Dempster DW 2021 Treatment of postmenopausal osteoporosis patients with teriparatide for 24 months restores forming bone quality indices to premenopausal healthy control values. ASBMR, October 1 – 4, Virtual Event, abstract A21023569 and oral presentation

1627. Hedjazi G, Guterman-Ram G, Blouin S, Hartmann MA, Schemenz V, Wagermaier W, Fratzl P, Zwerina J, Fratzl-Zelman N, Marini JC 2021 Novel murine model of atypical type VI osteogenesis imperfecta has altered matrix mineralization, osteocyte canalicular network and disordered collagen orientation. ASBMR, October 1 – 4, Virtual Event, abstract VPP-703 and poster presentation

1628. Fratzl-Zelman N, Hartmann MA, Zwerina J, Blouin S 2021 Bone mineralization density distribution and bone volume in adults with XLH after 48 weeks of Burosumab treatment: a paired biopsy study. ASBMR, October 1 – 4, Virtual Event, abstract A21023570 and poster presentation

1629. Liu Y, Hefferan T, Fratzl-Zelman N, Marini JC 2021 Bone cell functions in peptidylprolyl cis-trans isomerase B (PPIB) knock-out mouse model for type IX osteogenesis imperfecta (OI) are Distinct from Classical Dominant OI. ASBMR, October 1 – 4, Virtual Event, abstract VPP-707 and poster presentation

1630. Weigl M, Kocijan R, Ferguson J, Leinfellner G, Heimel P, Feichtinger X, Pietschmann P, Grillari J, Zwerina J, Redl H, Hackl M 2021 Characterization of circulating miRNAs during bisphosphonate and teriparatide treatment in ovariectomized rats. ASBMR, October 1 – 4, Virtual Event, abstract A21023559 and poster presentation

1631. Medibach A, Haschka J, Behanova M, Feurstein J, Kocijan A, Resch H, Kritsch D, Distel A, Zwerina J, Kocijan R 2021 Nutritional habits of patients with rare bone diseases & osteoporosis. Osteoporoseforum, October 14 – 16, St. Wolfgang, Austria, abstract and poster presentation

1632. Kraus DA, Haschka J, Behanova M, Huber S, Bartko J, Schanda JE, Meier P, Bahrami A, Zandieh S, Zwerina J, Kocijan R 2021 Fractal-based analysis of bone microarchitecture in Crohn's disease: a pilot study. Osteoporoseforum, October 14 – 16, St. Wolfgang, Austria, abstract and poster presentation

1633. Kraus DA, Haschka J, Huber S, Schanda JE, Behanova M, Meier P, Bahrami A, Zandieh S, Muschitz C, Resch H, Mähr M, Rötzer K, Uyanik G, Zwerina J, Kocijan R 2021 Analysis of bone architecture using fractal-based TX-Analyzer™ in adult patients with osteogenesis imperfecta. Osteoporoseforum, October 14 – 16, St. Wolfgang, Austria, abstract and poster presentation

1634. Feurstein J, Hadzimuratovic B, Behanova M, Haschka J, Rötzer K, Uyanik G, Witsch-Baumgartner M, Schett G, Zwerina J, Kocijan R 2021 Identifying adult hypophosphatasia in the rheumatology unit. Osteoporoseforum, October 14 – 16, St. Wolfgang, Austria, abstract and poster presentation

1635. Behanova M, Haschka J, Reichardt B, Dimai HP, Zwerina J, Kocijan R 2021 Incidence and mortality risk after pelvic fracture in Austria, 2010-2018. Osteoporoseforum, October 14 – 16, St. Wolfgang, Austria, abstract and poster presentation

1636. Stockinger T, Behanova M, Reichardt B, Haschka J, Resch H, Zwerina J, Kocijan R 2021 Adherence to anti-osteoporotic drugs during COVID-19-pandemic in Austria. Osteoporoseforum, October 14 –16, St. Wolfgang, Austria, abstract and poster presentation

1637. Messner Z, Carro-Vaquez D, Haschka J, Hackl M, Resch H, Muschitz C, Pietschmann P, Zwerina J, Kocijan R 2021 Circulating miRNAs respond to treatment with denosumab after two years in women with postmenopausal osteoporosis – the MiDeTe-study. Osteoporoseforum, October 14 –16, St. Wolfgang, Austria, abstract and poster presentation

7.1.3 Invited talks

V596 Kocijan R 2020 Osteoporose. Forum Innere Medizin, 2. Dezember (2020)

V597 Behanova M 2021 ÖVOS-II: Hip fracture and diabetes; ÖVOS-III: Pelvic fractures. Dachverband der Sozialversicherungsträger, 24. Februar

V598 Kocijan R 2021 Versorgung von Osteoporose-PatientInnen in Zeiten des Lockdowns. Osteologie 2021, Bremen, Deutschland (Hybridveranstaltung), 18. – 20. März

V599 Kocijan R 2021 XLH/Phosphatdiabetes – Eine lebenslange Erkrankung. Jahrestagung ÖGES (virtueller Kongress), 22. April

V600 Zwerina J 2021 Kollagenosen: Neue Kriterien, neue Therapieoptionen. 19. Wachauer Rheumatag, 24. April

V601 Zwerina J 2021 Gicht: Eine hochrelevante Systemerkrankung. Update Gastroenterologie-Stoffwechsel, Innsbruck, Österreich, 11. – 13. November

V602 Zwerina J 2021 Das neue Zentrum für seltene Knochenerkrankungen im Hanusch-Krankenhaus stellt sich vor. ÖGR Jahrestagung, 25. - 27. November, Wien, Österreich

V603 Kocijan R 2021 Seltene Knochenerkrankungen in der osteologischen Ambulanz. ÖGR Jahrestagung, 25. - 27. November, Wien, Österreich

8 Danksagung

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