Bone Abstracts

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Abstract book

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Invited Speaker Abstracts and Biographical Notes

IS1

Fetal development

Yasemin Alanay

Department of Pediatrics, Acibadem University School of Medicine, Istanbul, Turkey

The human long bones are subject to multiple changes *in utero* based on a cascade of pathways and cellular signaling mechanisms. In endochondral ossification, cartilage is gradually replaced by bone, beginning with diaphyseal ossification at 8 weeks of gestation. The epiphyses located at both ends between the joint and the primary physis (growth plate) are initially cartilaginous and later develop secondary ossification. The primary physis is responsible for longitudinal growth, and the newest bone forms the metaphysis. The secondary physis provides spherical growth of the epiphyseal ossification center. The diaphyseal diameter enlarges by means of bone deposition from the surrounding periosteum, and the diameter of the physis increases because of bone deposition from the perichondrium. In addition, the ossified components undergo bone marrow transformation. Any disturbances of epimetaphyseal development may result in various skeletal abnormalities. Skeletal patterning begins in the embryo, it is during fetal development that bone formation and mineralization accelerate. The formation of cartilage from stem cells during development is a complex process, which is regulated by both local growth factors and biomechanical cues, and results in the differentiation of chondrocytes into a range of subtypes in specific regions of the tissue. In fetal development cartilage also acts as a precursor scaffold for many bones, and mineralization of this cartilaginous bone precursor occurs through the process of endochondral ossification. In the endochondral formation of bones during fetal development the interplay between cell signalling, growth factors, and biomechanics regulates the formation of load bearing bone, in addition to the joint capsule containing articular cartilage and synovium, generating complex, functional joints from a single precursor anlagen. During embryonic development most of the skeleton begins as a cartilaginous scaffold that is progressively resorbed and replaced by bone. Endochondral bone development continues until the growth plates fuse during puberty. Growth and mineralization of the skeleton are dependent upon the adequate delivery of mineral. During fetal development, the placenta actively transports calcium, magnesium and phosphorus from the maternal circulation. In this talk, the timeline of fetal bone development and regulation will be summarized.

Disclosure

The author declared no competing interests.

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Biographical details

Dr Yasemin Alanay, MD, PhD is a Pediatric Geneticist, Professor of Pediatrics at Acibadem University School of Medicine, Istanbul. She studied medicine at Hacettepe University, Ankara, completed her residency in Pediatrics in 2002. Completed Pediatric Genetics Fellowship at Hacettepe Ihsan Dogramaci Children's Hospital. In 2006, she was mentored by Prof. D Rimoin and Prof. D Krakow as a research fellow at the International Skeletal Dysplasia Registry, Cedars Sinai Medical Center, Los Angeles, USA. She later received her PhD in Genetics in 2009 at Hacettepe University. She has participated and led research in the field of genetic diseases of skeleton and craniofacial malformations. Dr Y Alanay has authored over 95 peer-reviewed scientific publications and book chapters. She is a board member of ESHG and editorial boards of the American Journal of Medical Genetics and Clinical Dysmorphology. Her current practice involves clinical genetics, dysmorphology with a special interest in clinical, molecular, and social aspects of skeletal dysplasias.

IS2

Bone and osteocyte biology: lessons from human genetic diseases

Brendan Lee

Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, USA

Human skeletal dysplasias consist of over 450 distinct conditions that affect the development and maintenance of bone and cartilage. Broadly they can be characterized by those that affect primarily bone, i.e., the osteodysplasias, vs those that affect cartilage, i.e., the chondrodysplasia. However, the lines dividing these two are increasingly blurred as we recognized them to be a spectrum of osteochondrodysplasias. Importantly, the advent of next generation sequencing has led to increasingly complex genotype–phenotype correlations that now provide unprecedented insight into the important genetic determinants of bone and osteocyte biology. Increasing locus and allelic heterogeneity in association with phenotypic expansion are now informing new mechanistic hypotheses on how the skeletal progenitor cell commits to the osteoblastic lineage and eventually terminally differentiating into the osteocyte. Not surprisingly, we find that this process integrates differential contribution of classical signaling pathways into a rheostat that is highly context and time dependent. Moreover, autocrine, paracrine, and endocrine signaling further integrates cell–cell communication among all of the components within the bone niche.

Disclosure

Receipt of honoraria/consulting fees: Biomarin.

DOI: 10.1530/boneabs.4.IS2

Biographical details

Dr Brendan Lee is the Robert and Janice McNair Endowed Chair in Molecular and Human Genetics, Professor and Interim Chairman of the Department of Molecular and Human Genetics at Baylor College of Medicine. Dr B Lee co-directs the joint MD Anderson Cancer Center and Baylor College of Medicine Rolanette and Berdon Lawrence Bone Disease Program of Texas, and the Baylor College of Medicine Center for Skeletal Medicine and Biology. He is Founder and Director of the Skeletal Dysplasia Clinic at Texas Children's Hospital, and of the Medical Student Research Track at Baylor. As a pediatrician and geneticist, Dr B Lee studies structural birth defects and inborn errors of metabolism. Dr B Lee identified the first genetic causes of human skeletal dysplasias that affect the growth and strength of the skeleton. Most recently, he discovered new causes of brittle bone disease in children. In so doing, he is developing new approaches for diagnosing and treating these disorders.

IS3

Bone material properties

Peter Fratzl

Department of Biomaterials, Max Planck Institute of Colloids and Interfaces, Potsdam, Germany

Our skeleton needs to carry the body weight and to resist mechanical impacts. This capability or, conversely, bone fragility are controlled by the amount of bone mass, the shape and internal architecture of the bones, as well as by the material of which they are built. Bone material consists of a complex multi-scale arrangement of mineralized collagen fibrils containing also water, proteoglycans as well as some non-collagenous proteins. This organization is by no means constant during our life time. It changes with growth and bone maturation but even adult bone is constantly remodeled and, thus, able to repair damaged tissue and to adapt to the loading situation. In preventing fractures, the most important mechanical property is toughness, which is the ability to absorb impact energy without reaching complete failure. There is no simple explanation for the origin of the toughness of bone material and this property depends in a complex way on the internal structure of the material on all scales from nanometers to millimeters. Hence, fragility may have different structural origins, depending on which toughening mechanism is not working properly. The lecture reviews current knowledge about the multi-scale structure and quality of bone material appearing in humans and in animal disease models during bone growth, remodeling and healing, and discusses its putative relation to bone fragility.

Disclosure

Receipt of grants/research support: Lion Corporation, Japan.

DOI: 10.1530/boneabs.4.IS3

Biographical details

Peter Fratzl is director at the Max Planck Institute of Colloids and Interfaces in Potsdam, Germany, and honorary professor at Humboldt University Berlin and Potsdam University. He holds an engineering degree from Ecole Polytechnique in Paris, France, and a doctorate in Physics from the University of Vienna, Austria. His scientific interests include the relation between structure and mechanical behaviour of biological and bio-inspired materials, with a special focus on bone material structure and properties in osteoporosis treatment and bone regeneration. P Fratzl has been external member and advisor to the director of the Ludwig Boltzmann institute of Osteology in Vienna, Austria, for the last 20 years. He has published over 450 peer-reviewed research publications. He is Fellow of Acatech, the Austrian Academy of Sciences and the Materials Research Society (US), holds an honorary doctorate from Montpellier University and is recipient of the Leibniz Prize from the German Science Foundation.

IS4

Vertebral fracture assessment

Amaka C Offiah

University of Sheffield, Sheffield, UK

Osteoporotic fractures of the vertebrae are often silent and if left untreated will lead to progressive loss of vertebral body height and significant kyphoscoliosis, with its associated morbidity. However if vertebral fractures (VF) are detected early, treatment with bisphosphonates accelerates healing of prevalent fractures and reduces incident fractures. A survey of members of the British Paediatric and Adolescent Bone Group showed that treatment is started when two or more VF are diagnosed, therefore children with long-term conditions predisposing them to VF undergo routine regular surveillance. It follows that a simple, reliable, objective, low radiation, and cost-effective method of VF assessment (VFA) is required. No current method fulfils all these criteria for VFA in children.

Traditionally, diagnosis of VF is from lateral spine radiographs, however we have shown (funded by the National Institute for Health Research under its Research for Patient Benefit Programme (grant reference number PB-PG-0110-21240)) that dual energy X-ray absorptiometry (iDXA) is able to replace radiographs for diagnosis of VF at an average 28% of the radiation exposure. We demonstrated the poor ability of both iDXA and radiographs to differentiate mild VF from normal physiological variation; the absence of an objective external gold standard was a further confounder, complicating our cost-effectiveness analysis, and raising the question, 'does iDXA really miss fractures or does spine radiography overcall them?'

Existing scoring systems for adult VFA have been tried or modified and novel systems developed for use in children, however there is no standardisation and although prevalence of mild fractures is relatively low in published papers, observer reliability is variable.

Semi-automated VFA is used in adults, with a number of software tools available, including SpineAnalyzer (Optasia Medical Ltd). Our on-going trial (funded by the University of Sheffield Faculty Innovation Fund) in children using SpineAnalyzer suggests that it reduces interobserver variability, but leads to incorrect interpretation. The latter is not surprising since outcome is based on standards developed for adult vertebrae; significant physiological changes in vertebral morphometry occur throughout childhood, which would need to be captured before similar VFA software can be used reliably in children.

Funding

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Disclosure

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DOI: 10.1530/boneabs.4.IS4

Biographical details

Amaka C Offiah is Senior Lecturer and Consultant Paediatric Radiologist at the University of Sheffield and Sheffield Children's Hospital. She has a specialist interest in the musculoskeletal system. She has co-authored two books, seven book chapters, published 67 peer-reviewed articles and given over 100 invited national and international lectures. She is Convenor of the Skeletal Dysplasia Group for Teaching and Research and Chairperson of the European Society of Pediatric Radiology Child Abuse Taskforce. She was the RCR 2013 Roentgen Professor – being the first female and the first pediatric radiologist to hold this post.

IS5

High resolution imaging of bones by high-resolution peripheral quantitative computed tomography

Steven Boyd

McCaig Institute for Bone and Joint Health, University of Calgary, Calgary, Alberta, Canada

High-resolution peripheral quantitative computed tomography (HR-pQCT) provides a non-invasive measure of 3D micro-architecture at a nominal isotropic resolution of 82 μm, and more recently 61 μm with the new generation of scanners. The typical measurement site is at the peripheral skeleton, including the distal radius and distal tibia. The measurement is performed in <2 min now, and radiation dose is low for each scan (~ 5 μSv). Since it's introduction in 2005, there are many studies that have used this technology to explore natural variations in bone microarchitecture between men and women and across the lifespan, the influence of disease on bone microarchitecture, and the effects of interventions including anti-osteoporosis treatments. Owing to the low radiation dose, the technology is suitable for measurements in children, and has been used to show growth patterns in youth, and explore whether there is a difference in microarchitecture in children who sustain fractures during periods of rapid growth. There are challenges, however, to performing measurements in youth, and these will be discussed. This presentation will describe the technology and its applications, and the use of analysis techniques for these complex data. This includes strategies to maximize longitudinal measurement precision using methods such as 3D image registration, and the use of computer methods such as the finite element analysis to provide a non-invasive estimate of bone strength. The recent introduction of the second generation of HR-pQCT scanners provides new opportunities for assessment of bone, and some recent data on measurements at joints such as the knee will be presented. The study of *in vivo* bone microarchitecture provides a basis to assess individual patient bone strength, understand natural changes through the lifespan, monitor disease processes, and understand the role of interventions (physical exercise or pharmaceutical treatment) on bone microarchitecture. In summary, the introduction of new HR-pQCT technology offers exciting new opportunities for the study of bone quality.

Disclosure

Receipt of grants/research support: Merck Canada, Amgen.

DOI: 10.1530/boneabs.4.IS5

Biographical details

Dr Steven Boyd holds a PhD in Mechanical Engineering, specialized in Biomedical Engineering. He was appointed as a faculty member at the University of Calgary in 2002, and is now a Professor in the Faculty of Medicine (Radiology), and jointly appointed at the Schulich School of Engineering (Mechanical Engineering) and Faculty of Kinesiology. He is a principal investigator at the McCaig Institute for Bone and Joint Health in Medicine, and his research uses a multi-disciplinary biomedical engineering approach for development of early detection and monitoring of bone and joint health, with particular focus on osteoporosis and osteoarthritis. The Bone Imaging Laboratory he established in 2004 develops methods for bone quality detection using high-resolution computed tomography and computer methods such as the finite element analysis to investigate bone and joint diseases. He holds an Alberta Innovates – Health Solutions (AIHS) Senior Scholar position, and was appointed in 2010 as the Bob and Nola Rintoul Chair in Bone and Joint Research. His research is supported by the Canadian Institutes for Health Research, the Natural Sciences and Engineering Research Council (NSERC) of Canada, Canada Foundation for Innovation and AIHS.

IS6

Classical osteogenesis imperfecta

Nick Shaw

Department of Endocrinology and Diabetes, Birmingham Children's Hospital, Birmingham, UK

The 'classical' forms of osteogenesis imperfecta (OI) are those associated with the original Sillence classification of four types described in 1979. They account for 85–90% of all types of OI with the majority due to mutations in the genes for type 1 collagen, COL1A1 and COL1A2, and are usually dominantly inherited. They represent a significant spectrum of severity ranging from individuals with infrequent fractures, normal mobility and function to those with recurrent fractures, bone deformity and short stature with limited ambulation and function. Although more severely affected children will require significant input from a variety of professionals within a multidisciplinary team it is important to recognise that children with 'mild OI' may also have significant problems, e.g. the development of vertebral fractures.

An important time for all families with an affected child is the initial diagnosis and provision of appropriate information and support. This can have a significant impact on the subsequent attitude and behaviour of the family towards their child, which may compromise their future potential. This can lead to challenges in the management of such children by the OI team. Appropriate liaison and provision of information to schools is equally important. Another important time is transition to adult care, which is often significantly different in pattern to paediatric care. This requires a dedicated transition process, which should commence at entrance to secondary school.

Although significant advances have been made in the care of children and adolescents with 'classical OI' in the past 20 years with the availability of bisphosphonate treatment it is clear that there remain many problems. These include continued long bone fractures, development of scoliosis, and limitations in mobility and function. Such problems require the input of a broad multidisciplinary team that includes physicians, orthopaedic surgeons, specialist nurses, physiotherapists, occupational therapists, psychologists, and social workers.

Disclosure

Receipt of honoraria or consultation fees: Consilient, Alexion.

DOI: 10.1530/boneabs.4.IS6

Biographical details

Dr Nick Shaw is a Consultant Paediatric Endocrinologist at Birmingham Children's Hospital and Honorary Senior Clinical Lecturer at the University of Birmingham. He developed an interest in paediatric calcium and bone metabolism whilst a Lecturer at the University of Leeds in 1985 and subsequently as a Lecturer at the University of Liverpool. He completed his endocrine training in Birmingham where he has been a consultant since 1994. He established a multidisciplinary service for children with metabolic bone disease, which in 2011 was designated as one of four national centres for complex childhood osteogenesis imperfecta. He is the organiser of a postgraduate training course in paediatric calcium and bone metabolism and co-editor of the book 'Calcium and Bone Disorders in Children and Adolescents' published by Karger in 2009. He was a founder member and first secretary of the British Paediatric and Adolescent Bone Group and the Bone Club of the European Society for Paediatric Endocrinology. His research interests include secondary osteoporosis in children and vitamin D.

IS7

Recessive osteogenesis imperfecta

Frank Rauch

Shriners Hospital and McGill Unversity, Montreal, Quebec, Canada

Osteogenesis imperfecta (OI) is usually caused by dominant mutations affecting one of the two genes that code for two collagen type 1, but a recessive form of OI is present in 5–10% of individuals with a clinical diagnosis of OI. Most of the involved genes code for proteins that play a role in the processing of collagen type 1 protein (*BMP1, CREB3L1, CRTAP, LEPRE1, P4HB, PPIB, FKBP10, SERPINF1, SERPINH1, PLOD2, SEC24D*, and *TMEM38B*), or interfere with osteoblast function (*LRP5, SP7*, and *WNT1*). Mutations in these genes usually lead to severe recessive OI that on clinical evaluation is often difficult to distinguish from OI caused by dominant mutations. However, specific phenotypes are caused by mutations in *SERPINF1* (recessive OI type VI), *P4HB* (Cole-Carpenter syndrome) and *SEC24D* ('Cole-Carpenter like'). For most of these new gene defects the mechanisms linking mutation to phenotype remain to be elucidated. Thus, over the past decade, at least 15 genes have been associated with recessive OI.

Disclosure

Receipt of grants/research support: Novartis, Alexion; receipt of honoraria or consultation fees: Genzyme.

DOI: 10.1530/boneabs.4.IS7

Biographical details

Dr Frank Rauch obtained his MD degree from the Technical University of Munich, Germany, and trained as a pediatrician at the Children's Hospital of Cologne University, Germany. Since 2001 Dr F Rauch has been a clinician-scientist at the Shriners Hospital for Children and is currently a Professor of Pediatrics at McGill University, Montreal, Canada. His clinical and scientific work focuses on heritable bone diseases in children and adolescents, in particular osteogenesis imperfecta. He is the Director of Clinical Laboratories at Shriners Hospital, comprising laboratories for biochemistry, bone histomorphometry, and molecular diagnostics. Dr F Rauch has published more than 160 original articles in peer-reviewed scientific journals. Since 2009, he has been Editor-in-Chief of the Journal of Musculoskeletal and Neuronal Interactions.

IS8

Early-onset osteoporosis

Outi Mäkitie[1,2,3]

[1]Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; [2]Department of Clinical Genetics, Karolinska University Hospital, Stockholm, Sweden; [3]Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Genetic factors play an important role in the development of osteoporosis. Several monogenic forms of osteoporosis have been recognized. The most common of these is osteogenesis imperfecta (OI) in which mutations in the genes encoding type 1 collagen (*COL1A1* and *COL1A2*) are responsible for ~90% of the cases. Several rare autosomal recessive forms of OI have also been described. In these the defects lie in proteins involved in posttranslational modification of type 1 collagen. Recent discoveries have further elucidated the genetic determinants of early-onset skeletal fragility and several forms not related to type 1 collagen have been identified.

The canonical WNT-signalling pathway is considered to be of key importance for skeletal health, activation leading to increase and inhibition leading to decreased bone mass. Loss-of-function mutations in *LRP5*, encoding a co-receptor for the pathway, cause the autosomal recessive osteoporosis–pseudoglioma syndrome. Carriers of *LRP5* mutations also have reduced bone mass and present with early-onset osteoporosis and compression fractures. *LRP5* polymorphisms associate with peak bone mass, BMD and fractures in the general population, highlighting the significance of this gene in bone mass development and maintenance. Recently heterozygous loss-of function mutations in the *WNT1* gene were shown to lead to early-onset osteoporosis while homozygous *WNT1* mutations resulted in severe infancy-onset osteoporosis. These findings suggest that WNT1 is a key ligand for the WNT-signalling pathway in the regulation of bone mass.

The first X-chromosomal form of osteoporosis, resulting from mutations in the gene encoding plastin 3 (*PLS3*), was described in 2013. PLS3 is involved in actin bundle formation in the cytoskeleton. PLS3–osteoporosis has its onset in childhood and is characterized by recurrent peripheral fractures, low BMD, vertebral compression fractures, and significant height loss in adulthood. Males are in general more severely affected than females. The mechanism whereby PLS3 affects bone health is unclear, but it may be linked to osteocyte dendrite function and skeletal mechanosensing. Future studies are needed to elucidate the role of *WNT1* and *PLS3* in early-onset osteoporosis and to define optimal therapy for affected individuals. It is likely that further genetic studies in families with early-onset osteoporosis will identify other genes and pathways that play a role in childhood-onset osteoporosis.

Disclosure

The author declared no competing interests.

DOI: 10.1530/boneabs.4.IS8

Biographical details

Dr. Outi Mäkitie received her MD and PhD from the University of Helsinki, Finland where she also completed training in Pediatrics and in Pediatric Endocrinology. After a 3-year post-doctoral clinical and research fellowship at The Hospital for Sick Children in Toronto, Canada, she returned to Finland and served as Head of the Metabolic Bone Clinic, Children's Hospital, University of Helsinki. In 2013 she moved to Stockholm, Sweden and currently works as Associate Professor at Clinical Genetics, Karolinska Institutet and Karolinska University Hospital. Dr O Mäkitie's clinical and translational research focuses on various genetic and acquired skeletal disorders.

IS9

Upper limb deformity in osteogenesis imperfecta

Marie Gdalevitch

Montreal, Quebec, Canada

The objectives of this talk are to discuss the assessment, management, and operative indications of upper limb deformities in osteogenesis imperfecta (OI). The indications for operative treatment of upper limb deformities have evolved with the advent of improved medical treatment (bisphosphonates) and long bone rodding in the lower extremities. Long bone rodding in the lower extremities has become standard treatment in OI. However, upper limb deformities are less commonly treated surgically due to lack of clear indications, limited surgical experience with these challenging deformities and the false impression that the upper extremities are non-weight bearing.
Children with moderate to severe OI types have become more mobile due to improved medical and surgical treatment and may require the use of their upper limbs to initiate and maintain walking as well as for activities of daily living. Ambulatory patients with moderate to severe OI use walking aids and therefore will be applying increase weight on their upper limbs for support. As such, upper limb deformities and fractures have become a more significant problem and can impact function and quality of life in these patients.
Upper extremity deformities in OI are becoming an increasing problem and are surgically more challenging to treat due to the size of the bones and the extent of the deformities. The proximal upper limb (i.e., the humerus) is more commonly addressed surgically in upper limb deformities. Deformities of the proximal humerus are typically easier to correct than those in the distal third of this bone. A common complication of osteotomies in the distal third of the humerus is non-union with development of a pseudarthrosis. Surgical techniques for rodding the humerus as well as methods to avoid and treat a variety of complications will be discussed. The need for additional fixation in humeral deformity correction will also be addressed. The presentation will then examine deformities of the elbow, including radial head dislocations and the conservative and surgical treatment options available to improve elbow function. Finally, indications for surgical correction of forearm deformities will be addressed along with guidelines for treatment of forearm deformities in OI.

Disclosure

Educational consultant: Smith and Nephew.

DOI: 10.1530/boneabs.4.IS9

Biographical details

Dr Marie Gdalevitch completed both her medical and orthopedic surgery degrees at McGill University. Following her residency, Dr M Gdalevitch pursued her first fellowship in limb lengthening and deformity correction at the International Center for Limb Lengthening in Baltimore, Maryland. Dr M Gdalevitch then embarked on her second fellowship in pediatric orthopedics and basic science research at the Children's Hospital at Westmead in Sydney, Australia. She is currently an assistant professor of surgery in the Division of Orthopedics at McGill University and works at the Shriners Hospital in Montreal as well as the Montreal General Hospital. Her clinical interests include: limb lengthening and deformity correction, osteogenesis imperfecta, hip reconstruction, and pediatric orthopedics. Dr M Gdalevitch is currently pursuing a PhD in bone regeneration research involving murine models of distraction osteogenesis well as disuse osteopenia models.

IS10

NF-1 bone biology and pseudoarthrosis

David Little

Centre for Children's Bone and Musculoskeletal Health, Kids Research Institute, The Children's Hospital at Westmead, University of Sydney, Sydney, New South Wales, Australia

Tibial dysplasia, which leads to fracture and pseudarthrosis, occurs in around 4% of children with NF1, and also in children with no underlying disorder. Pseudarthrosis of the fibular may or may not be present, or as an isolated entity, as can pseudarthrosis in the forearm (rare). Other bone problems faced by individuals with NF1 are scoliosis (20%), pectus excavatum/carinatum (12%), and sphenoid wing dysplasia (7%). Dural ectasia and plexiform neurofibromas can also affect the bone. The protein neurofibromin acts as a regulator of the Ras/MAPK pathway in all cells, and its loss leads to Ras overactivity.

An underlying bone phenotype has emerged: up to 30% of children with NF1 are osteopenic, with smaller bones and decreased stress–strain index. While bone homeostasis is often close to normal, bone healing at pseudarthrosis sites is grossly abnormal. Typically a low energy pathological fracture will occur in the anterolaterally bowed tibia, which will not heal despite immobilisation, with bone resorption and invasion of fibrous tissue dominating over bone formation. Stevenson and others have shown that in at least some psuedarthroses, loss of heterozygosity has occurred rendering the tissue $NF1^{-/-}$. We have created a model of local haploinsufficiency in a fracture by injecting NF1 floxed mice with a cre-bearing adenovirus. Much of the fibrous tissue that ensues is $NF1^{-/-}$. Non-union occurs in most animals, along with typical findings of excessive bone resorption and multiple TRAP-positive cells in the fibrous tissue.

We have taken a pathway approach and a generic approach to rescuing the model. In the pathway approach we have blocked downstream kinases in the overactive pathway, including MEK and JNK. MEK inhibition has the unwanted effect of inhibiting endochondral ossification. JNK inhibition, especially when combined with BMP2, produces a high rate of union and a decrease in the amount of fibrous tissue. The generic approach of boosting bone formation with BMP2 and inhibiting resorption with zoledronic acid is also effective, with a high rate of union and reduced fibrous tissue invasion. Further translational work is required to conquer tibial pseudarthrosis and the accompanying disability it creates for children.

Disclosure

Receipt of grants/research support: Novartis, Amgen, Celgene, N8.

DOI: 10.1530/boneabs.4.IS10

Biographical details

Prof. David Little received his Medical Degree from the University of Sydney where he is Conjoint Professor of Paediatrics and Child Health, specialising in Orthopaedic Surgery. Prof. D Little is Head of Orthopaedic Research and Biotechnology at The Children's Hospital at Westmead, part of the Sydney Children's Hospital Network. He has broad clinical interests in Children's Orthopaedic Surgery, and has specific expertise in lower limb problems including hip disorders and limb lengthening and deformity correction. His research interests are into the pathophysiology of bone repair in NF1/congenital pseudarthrosis, Perthes disease, and other forms of avascular necrosis of the hip. He is also renowned for publications on fracture healing, including the role of therapeutic agents in augmentation of bone repair.

IS11

Recent advances in limb lengthening and deformity correction

John Herzenberg

Baltimore, Maryland, USA

External fixation has been the gold standard for patients who require bone lengthening. This method is accurate and reliable, but can result in significant scarring, superficial infection, and pain. Additionally, the daily care of pin sites, unsightly appearance of the device, and reduced function can be emotionally taxing for both the patient and caregivers. An internal device that lengthens through rotational movement was developed to address some of these issues (ISKD). Although cosmetically superior, the device was sometimes uncontrolled, which could lead to soft tissue contractures, healing problems, nerve injury, and excessive pain. In late 2011 a new, controllable internal device called the PRECICE (Ellipse Technologies, Irvine, CA, USA) was approved for use in the USA. We have used this device successfully in over 150 patients, aged 7–66. We conducted a study in which we administered a 13-question survey to patients who had experienced treatment with both external fixation and the PRECICE. Patients reported higher satisfaction rates with the PRECICE in regard to ease of physical therapy, cosmetic results, complications, day to day function, return to physical and social activity, and overall satisfaction. All patients stated that if they required surgery again, they would choose the PRECICE device. From a patient/parent perspective, this internal lengthening device rates far superior to external fixation. Participants felt that it resulted in less pain, fewer complications, and allowed for a quicker return to daily living. Although not everyone is a candidate for the PRECICE, it offers a promising alternative to previously available options.

Disclosure

Receipt of grants/research support: Ellipse Technologies; Receipt of honoraria/consultation fees: Orthopediatrics.

DOI: 10.1530/boneabs.4.IS11

Biographical details

Dr John Herzenberg graduated from Boston University Medical School and trained at Duke University for Orthopaedics and Toronto Sick Kids for Pediatric Orthopaedics. He specializes in the diagnosis and treatment of adult and pediatric patients with congenital abnormalities, joint contractures, neuromuscular disorders, non-unions, malunions, deformity, and bone defects. He is in demand worldwide as a speaker and has more than 110 PubMed papers listed to his credit. Dr J Herzenberg is married to Merrill Chaus, RN. They have three daughters. Since 1998, he and his family have volunteered yearly with Operation Rainbow, providing free orthopaedic surgery to underprivileged children in Central and South America, and Haiti. In 1997, Dr J Herzenberg learned an old, ignored conservative technique for clubfoot treatment called the Ponseti method. He enthusiastically embraced this method, and his efforts in teaching this method have helped turn the tide from surgery to casting for babies with clubfoot.

IS12

The role of TGFβ in high turnover bone diseases

Susan Schiavi

Boston, Massachusetts, USA

TGFβ is a family of ubiquitous growth factors that play a prominent role in bone biology. In normal bone remodeling, TGFβ1 released from the bone matrix by osteoclasts, attracts mesenchymal stem cells to sites of resorption thereby ensuring that new bone restores eroded older bone. TGFβ also promotes osteoblast proliferation but later restricts osteoblast maturation by repressing the expression of genes involved in bone formation. Recent evidence has demonstrated that inhibition of SMAD3 dependent TGFβ signaling is required for the decreased sclerostin expression that occurs in response to mechanical loading. Similar to other autocrine/paracrine factors, TGFβ's diverse activities on bone are dependent on regulation by negative and positive regulators that orchestrate specific TGFβ functions in a spatial and temporal manner. Emerging evidence suggests that dysregulation of this pathway and/or its regulators contribute to a variety of bone pathologies including renal Camurati–Engelmann disease, renal osteodystrophy, osteogenesis imperfecta, high turnover osteoporosis, and osteoarthritis. For example, TGFβ is elevated in serum, bone and other tissues of individuals with chronic kidney disease. In preclinical studies TGFβ neutralization normalized bone turnover markers, decreased bone formation, improved trabecular and cortical architecture and reduced cortical porosity in the setting of high turnover renal osteodystrophy. TGFβ neutralization decreased SOST mRNA expression and restored repressed β-catenin to normal levels as evidenced by enhanced expression of genes downstream of Wnt/β-catenin signaling. Since TGFβ is known for temporal actions on osteoblasts that first promote and then attenuate osteoblast differentiation, it is conceivable that continuous pathologic over-expression could be associated with sustained inhibition of osteoblast maturation as exemplified by changes in Wnt/β-catenin signaling. Further exploration of TGFβ's mechanism of action on renal and other bone diseases has been initiated using a network based informatic approach.

Disclosure

The author declared no competing interests.

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Biographical details

Susan Schiavi has spent her career as a research scientist within the biotech/pharmaceutical industry. She received her PhD from the University of Massachusetts Medical School and completed a postdoctoral fellowship at Harvard Medical School. As a Senior Scientific Director at Genzyme and Sanofi, her primary role has been the development of scientific strategy for the identification of novel therapeutic targets and translational research associated with genetic and acquired bone and renal diseases. Within this framework, her team's research incorporated a network based bioinformatics approach to complement traditional research strategies centered on the role of critical proteins associated with skeletal health. She has published more than 30 peer research articles, invited review articles, and book chapters.

IS13

Shared therapeutic targets in genetic skeletal diseases

Michael D Briggs, Katarzyna A Pirog & Peter A Bell

Institute of Genetic Medicine, International Centre for Life, Newcastle University, Newcastle-upon-Tyne, UK

Genetic skeletal diseases (GSDs) are an extremely diverse and complex group of rare genetic diseases that primarily affect the development and homeostasis of the osseous skeleton. There are more than 450 unique and well-characterised phenotypes that range in severity from relatively mild to severe and lethal forms. Although individually rare, as a group of related genetic diseases, GSDs have an overall prevalence of at least 1/4000 child. Qualitative defects in cartilage structural proteins, such as collagens, proteoglycans and glycoproteins, result in a broad spectrum of both recessive and dominant GSDs.

Over the last 10 years the analysis of mouse models for *COL2A1*, *COL10A1, MATN3*, *COMP*, and *ACAN* mutations have been performed in detail, which has allowed a direct comparison of disease mechanisms. Furthermore, the application of -omics based investigations (mRNA and protein) has allowed disease signatures to be derived and either shared or discrete downstream genetic pathways to be identified. A common feature in many of these mouse models was evidence of endoplasmic reticulum (ER) stress, translating in some cases to a reduction in chondrocyte proliferation and an increase in dysregulated apoptosis in the growth plate.

Defining the relative contribution of reduced proliferation, increased and/or dysregulated apoptosis to growth plate dysplasia and reduced bone growth is experimentally challenging; however, the study of novel 'ER-stress phenocopies' has recently provided new insight into the specific impact of these different disease mechanisms. The cartilage-specific expression of mutant forms of thyroglobulin has confirmed that reduced chondrocyte reduction, in the absence of perturbations to apoptosis, was sufficient to cause a significant reduction in long bone growth.

In summary, recent studies using a complimentary group of genetically relevant mouse models and cartilage specific knock outs have demonstrated the key role that ER stress plays in the initiation and progression of growth plate dysplasia and reduced bone growth in a range of different GSDs. Moreover preliminary studies suggest that ER stress is therapeutic target that can be influenced through small molecule intervention.

Disclosure

The author declared no competing interests.

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Biographical details

Michael D Briggs obtained his PhD at the MRC Clinical Research Centre, Harrow, studying the genetic basis of osteogenesis imperfecta. He undertook postdoctoral work at UCLA identifying the genetic basis of chondrodysplasias. In 1996 Mike moved to Manchester as an AR-UK Fellow to continue studying disease mechanisms in chondrodysplasia. In 2004 he was awarded a Wellcome Trust Senior Research Fellowship that was renewed in 2009. In 2012 he was appointed Professor of Skeletal Genetics in the Institute of Genetic Medicine at Newcastle University and continues to work on disease mechanisms in chondrodysplasia with a focus on identifying novel therapeutics for these rare diseases. Mike has been instrumental in establishing several European consortia for the diagnosis and research of rare skeletal diseases. These have included European Skeletal Dysplasia Network, EuroGrow and most recently SYBIL, a large-scale FP7 funded project involving 18 partners over 5 years.

IS14

Somatic mosaic skeletal overgrowth disorders

Matthew L Warman

Boston Children's Hospital, HHMI, and Harvard Medical School, Boston, MassachusettsUSA

I will describe non-cancerous skeletal diseases that occur as a consequence of somatic mutation. I will introduce the work of Drs Mary Lyon, Dorothea Bennett, and Rudolf Happle that provided insights into the mechanism responsible for several genetic, non-heritable diseases. I will then describe the technology and analytic strategies that several laboratories, including my own, employed to identify mutations in patients with Maffucci, Proteus, CLOVES, and Klippel-Trenaunay syndromes, Ollier disease, and macrodactyly. Many presumed somatic mosaic skeletal conditions, such as Gorham-Stout disease, remain unsolved and I will mention the obstacles that have, thus far, kept labs from discovering their causes.

The remainder of my talk will be focused on somatic *PIK3CA* mutations, which unexpectedly – to me at least – are associated with a wide spectrum of clinical phenotypes. I will detail how we have been using droplet digital PCR (ddPCR) and single molecule molecular inversion probes (smMIPs) to search for low abundance mutations in patients. I will also describe approaches that employ model organisms to determine whether a somatic mutation is necessary and sufficient to cause disease and, if so, which component features of the disease can be prevented, delayed, or reversed. I will conclude by addressing treatment strategies for patients with malformations caused by *PIK3CA* somatic mutation.

Disclosure

The author declared no competing interests.

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Biographical details

Dr Matthew L Warman is the Harriet M Peabody Professor of Orthopaedic Surgery and Genetics at Harvard Medical School. He attended college at Brown University and Medical School at Cornell University. While in medical school, he performed research with Dr Adele Boskey at The Hospital for Special Surgery. After medical school he trained in Pediatrics at the Children's Hospital in Washington, DC, in Genetics at the Children's Hospital in Boston, and he performed post-doctoral research with Professor Bjorn R Olsen at Harvard Medical School. In 1994, Dr M L Warman established an independent laboratory and clinical program in the Department of Genetics and Center for Human Genetics at Case Western Reserve University and University Hospitals of Cleveland. In 2006, he returned to Boston to become director of the Orthopaedic Research Laboratories at Boston Children's Hospital. Dr M L Warman is also an investigator with the Howard Hughes Medical Institute. The patients and families, who Dr. M L Warman has come to know through his clinical work as a pediatrician and geneticist, have often served as the impetus for his research. In addition to working with patients and families, members of Dr M L Warman's lab try to understand and treat human disease by studying cultured cells, purified proteins, and other organisms. Having benefited from superb mentoring throughout his career, Dr M L Warman enjoys introducing students (from high school to professional school) to the importance and excitement of Human Genetics. He is proud to have mentored students at all levels, who have gone on to become excellent scientists, physicians, and educators.

IS15

Achondroplasia-new therapy

Laurence Legeai-Mallet

INSERM U1163, Imagine Institute, Paris Descartes University, Paris, France

Fibroblast growth factor receptor 3 (FGFR3) is an important regulator of bone formation. Achondroplasia (ACH) is the most common form of dwarfism; it involved *FGFR3* gene mutations, in which skull, appendicular and axial skeletons are affected. The comparative analyses of the skeletal phenotype of *Fgfr3* mice ($Fgfr3^{Y367C/+}$) and patients with ACH showed, in both cases, short stature, defective proliferation, and differentiation of the chondrocytes in the growth plate cartilage, skull base anomalies with a complete absence of the synchondrosis and a reduction of the size of the occipital foramen. Both endochondral and membranous ossification processes are disrupted during development in ACH and $Fgfr3^{Y367C/+}$ mice. At cellular level, *Fgfr3* gain-of-function mutations induce increased phosphorylation of the tyrosine kinase receptor FGFR3; which correlated with an enhanced activation of its downstream signaling pathways. Potential therapeutic strategies have emerged for ACH. Several preclinical studies have been carried out: C-type natriuretic peptide (CNP) analog (BMN111), intermittent PTH injections, soluble FGFR3 therapy, meclozine and statin treatments. Among the putative targets to antagonize FGFR3 signaling, CNP (or BMN111) is one of the most promising strategies. BMN111 acts as a key regulator of longitudinal bone growth by down-regulating the MAPK pathway, which is activated as a result of *FGFR3* gain-of-function mutation. Preclinical studies showed that BMN111 treatment led to a large improvement in skeletal parameters in $Fgfr3^{Y367C/+}$ mice. BMN111 is currently in clinical trial (phase 2) in pediatric patients with achondroplasia. Since the identification of the gene 20 years ago, the clinical trial marks the first big step toward real treatment for these patients.

Disclosure

The author declared no competing interests.

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Biographical details

Laurence Legeai-Mallet is currently Director of Research at Imagine Institute-Paris Descartes University. She received her PhD in genetic from University of Paris V, she is a member of International skeletal dysplasia Society, European Skeletal Dysplasia Network and the French reference center of bone dysplasias. She has been involved in the field of skeletal disease since 1993. Her research field ranges from identification of disease genes involved in cartilage and bone diseases, in understanding bone development and skeketal diseases to the development of therapeutic approaches. In 2009, she initiated therapeutic approaches for osteochondrodysplasias through collaboration in both academic chemistry laboratory (Paris Descartes University) and pharmaceutical companies. In 2012, in collaboration with BioMarin, she reported the therapeutic potential of a novel natriuretic peptide C analogue (BMN111) as the first investigational therapy for the most frequent dwarfism, achondroplasia.

IS16

Growth plate and diseases of calcinosis

Ken White

Indianapolis, Indiana, USA

The balance of phosphate handling is now realized to occur through endocrine communication between the skeleton and kidneys. Low serum phosphate leads to severe growth plate defects, whereas elevated serum phosphate results in ectopic calcification of the vasculature and soft tissues. Mendelian disorders and their orthologous mouse models involving defects of growth plate formation and of calcinosis have brought to light new and important information regarding bone formation and mineral ion handling. Recent work examining the molecular mechanisms causing heterogeneous diseases of mineral metabolism involving the loss of function in both FGF23 and genes that control the pyrophosphate/inorganic phosphate, such as ENPP1, has led to the possibility of layers of local communication within the bone and kidney endocrine axes. Loss of function mutations in FGF23 combined with genomic analyses identifying SNPs in modifier genes may reveal complex systemic interactions that dictate the severity of calcification phenotypes. Certainly, the combined undertaking of clinical, basic, and translational research approaches has produced the largest impact on determining the molecular events dictating extracellular phosphate and effects on bone structure and function. The events regulating the intracellular processing of hormones such as FGF23 in the context of testing direct glycosylation and phosphorylation, as well as the regulated cleavage and inactivation of this hormone, may reveal new control points in bone metabolism for therapeutic interventions in both rare disorders as well as in common diseases such as CKD. Finally, emerging therapies directly targeting defects in mineral metabolism may offer alternatives to standard therapies that only address downstream disease manifestations.

Disclosure

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Biographical details

Ken White, PhD is the David D Weaver Professor of Genetics in the Department of Medical and Molecular Genetics at the Indiana University School of Medicine in Indianapolis, IN, USA. He serves as Director of the Division of Molecular Genetics and Gene Therapy. Dr K White's research interests focus on the molecular genetics of metabolic bone diseases in regards to phosphate metabolism and control of FGF23. He is the recipient of the American Society for Bone and Mineral Research's 2007 Fuller Albright Award, and in 2013, Dr K White was named an inaugural IU School of Medicine Showalter Scholar. He is also a member of the IU Simon Cancer Center.

IS17

Molecular and cellular bases of high bone mass

Anna Villa[1,2]

[1]Milan Unit, Institute of Genetic and Biomedical Research (IRGB), National Research Council (CNR), Milan, Italy; [2]Humanitas Clinical and Research Center, Rozzano, Italy

Bone remodelling is maintained by a balanced activity of osteoclasts and osteoblasts. Alterations in this cross-talk result in bone pathological conditions. High bone mass defines a complex and heterogenous genetic condition characterized by increased bone density. In particular, osteopetrosis is a genetic condition of high bone mass caused by impairment in osteoclast generation or function. Molecular analysis of human osteopetrosis has allowed the identification of novel genes playing key roles in osteoclast function and generation. In my presentation, I will focus on the genes involved in the pathogenesis of the dominant and recessive forms of osteopetrosis. This disease is highly heterogeneous in presentation and is often misdiagnosed in the mild forms. To date, seven genes have been identified as being responsible for autosomal recessive osteopetrosis (ARO). In humans, mutations in *TCIRG1, CLCN7, OSTM1, SNX10*, and *PLEKHM1* molecules have been described to cause osteoclast-rich ARO in which osteoclasts are present but severely impaired in their ability to resorb bone. Conversely, mutations in *TNFSF11* and *TNFRSF11A* genes lead to osteoclast-poor ARO, characterized by the absence of multinucleated osteoclast. Mutations in the carbonic anhydrase II gene result in osteopetrosis associated with renal tubular acidosis, while mutations impairing the NFκB essential modulator (NEMO) gene have been reported in a rare X-linked syndrome characterized by increased bone density associated with anhidrotic ectodermal dysplasia, immunodeficiency, and lymphoedema. The molecular basis underlying the disease is crucial for the identification of the best therapeutic approach to offer to affected individuals.

Disclosure

The author declared no competing interests.

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Biographical details

Anna Villa is Chief of the Human Genome Unit at UOS/IRGB and is also responsible for a Research Unit at Telethon Institute for Gene Therapy (TIGET). Her group has also extensively contributed towards the molecular dissection of genetic bone disorders, focusing on autosomal recessive osteopetrosis (ARO). In particular she has identified TCIRG1 as the gene responsible for 60% of the ARO patients and contributed towards the characterization of two other forms of ARO due to a defect in the Grey Lethal and PLEKHM1 gene respectively. More recently her group has described RANKL and RANK as genes responsible for the osteoclast poor ARO. In addition, over the last 5 years, Dr A Villa's group has pioneered the use of the *oc/oc* model to test *in utero* cellular therapy; this has established that prenatal correction of the defect is possible, since almost complete rescue of the phenotype has been achieved. The contribution of Dr A Villa in the molecular dissection of ARO has important implications not only for the molecular diagnosis, but also for the treatment of the disease.

IS18

Management of sclerosing bone disease

Michael P Whyte

Center for Metabolic Bone Disease and Molecular Research, Shriners Hospitals for Children, St Louis, California, USA

Many disorders cause osteosclerosis, and many exclusively affect adults. Pediatricians are likely to encounter those that are Mendelian diseases, with most still classified as 'dysplasias' although now understood at the gene level. Thus, there is promise for defining their molecular and biochemical pathogeneses, and for developing targeted medical treatments. Sclerosing bone dysplasias too have become the 'turf' of the metabolic bone disease specialist. However, their clinical spectrum ranges broadly from autosomal dominant typically benign findings exemplified by Worth-type endosteal hyperostosis in adults due to LRP5 activation, to autosomal recessive severe sclerosteosis, van Buchem disease, or lethal types of infantile ('malignant') osteopetrosis (OPT) that require treatment. The causal genes regulate primarily the cells for bone apposition or for bone resorption; e.g., osteosclerosis from LRP5 activation with increased osteoblast activity, or the osteopetroses (OPTs) from impaired osteoclast (OC) formation or function.

The major treatment concern for pediatricians is infantile OPT. We know the pathogenesis of the skeletal disease for all genuine OPTs is a life-long block of OC-mediated bone resorption due to defects in various genes. Bone biopsy will confirm the failed OC action by showing unresorbed calcified primary spongiosa. Now, progress from the identification of causal genes for OPT has impacted importantly on potentially curative bone marrow transplantation (BMT) aimed to replace defective OCs. Most OPTs involve dysfunctional OCs that can be seen on bone histology, explaining why BMT therapy is useful. However, significant genetic heterogeneity now underlies the OPTs. In especially rare OPTs, the defective bone resorption is not intrinsic to the OC, but lies elsewhere (e.g., RANKL deficiency), and is not corrected by conventional BMT. Therefore, important distinction between 'OC-rich' and 'OC-poor' OPTs is now crucial when considering BMT treatment. Mutation analysis can distinguish the OPTs that should respond to BMT. Unfortunately, differences in the pathogeneses among the heritable OPTs can impact other organs, including the brain where there can be severe complications not alleviated by BMT. Despite restoration of bone resorption by BMT, these OPTs are nevertheless considered untreatable due to their neurological outcomes. Now, availability of potent antiresorptives presents the specter of iatrogenic OPT if these agents are administered excessively for other disorders of skeletal or mineral homeostasis in infants or children. For BMT directed at severe OPT, time is of the essence because ongoing nerve compression may cause irreversible neurological damage, and further marrow space crowding impairs engraftment of transplanted cells. Unfortunately, reports concerning the techniques for BMT in OPT are now outdated and misleading in terms of donor candidacy, engraftment rates, and graft vs host disease, etc. However, the newer preparative regimens for BMT continue to lack worldwide consensus and uniformity. For infantile OPT, hypocalcemia from blocked bone resorption before BMT can lead to distinctive signs, symptoms, and complications, and often requires pharmacologic treatment. Post-BMT OPT may 'paradoxically' require antiresorptive treatments as restoration of OC action leads temporarily to hypercalcemia. Medical approaches for severe OPT have included the pioneering efforts by Dr Lyndon Key to drive OCs using high-dose 1,25-dihydroxyvitamin D_3 together with a low calcium diet, but lacked validation and are losing favor. In contrast, his interferon gamma 1b treatment is having a resurgence of interest. Discovery of the chloride channel 7 defect underlying the one true form of autosomal dominant OPT (Albers-Schönberg disease) is leading to new therapeutic considerations for this often troublesome 'benign' OPT. This arena of treatment for sclerosing bone disease is dynamic, important, and a brief overview is the goal of my presentation.

Disclosure

The author declared no competing interests.

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Biographical details

Michael P Whyte is Professor of Medicine, Pediatrics, and Genetics at the Washington University School of Medicine, a staff member of Barnes-Jewish Hospital and St. Louis Children's Hospital, and Medical-Scientific Director at the Center for Metabolic Bone Disease and Molecular Research, Shriners Hospital for Children in St. Louis, Missouri, USA.

Dr Whyte earned his MD degree at Downstate College of Medicine, State University of New York, Brooklyn, New York and then had internship and residency training in Internal Medicine at Bellevue Hospital in New York City. After two years as Clinical Associate at the National Institutes of Health, Bethesda, Maryland, he did his fellowship in the Division of Bone and Mineral Diseases and joined the medical faculty of the Washington University School of Medicine, St. Louis, USA.

Dr Whyte's research interests include especially the cause, outcome, and treatment of heritable disorders of bone and mineral metabolism in children and adults. Included are genetic forms of rickets such as hypophosphatasia and X-linked hypophosphatemia, brittle bone diseases like osteogenesis imperfecta, conditions that cause dense bones such as osteopetrosis, and disorders of accelerated skeletal turnover including juvenile Paget's disease. The Research Center at Shriners Hospital serves as a national and international resource for the diagnosis, treatment, and investigation of disorders of bone and mineral metabolism and skeletal dysplasias in children. Laboratory investigations include searches for the underlying mutated genes of new disorders. Phenotype/genotype correlations aim to better understand the pathogenesis of established conditions. Bone-targeted alkaline phosphatase replacement therapy is being evaluated for pediatric patients with hypophosphatasia. Dr. Whyte has authored or coauthored more than 300 scientific papers or book chapters concerning these disorders.

IS19

Rare sclerosing bone dysplasias

Gen Nishimura

Department of Pediatric Imaging, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan

Sclerosing bone dysplasias (too much bone diseases) are divided into two major groups, one group caused by impaired bone resorption and the other by increased bone formation. The former comprises a group of osteopetrosis (disorders due to abnormal osteoclastogenesis or osteoclast dysfunction) with relatively homogeneous skeletal phenotypes. By contrast, the latter encompasses a complex group of disorders with heterogeneous pathogeneses and diverse skeletal phenotypes.
From the pathogenic viewpoint, the latter group is classified into several groups: i) a group of abnormal Wnt signaling (AD osteopetrosis type 1/endooseal hyperostosis Worth type, van Buchem disease, and sclerosteosis, osteopathia striata with cranial sclerosis, a subset of craniodiaphyseal dysplasia), ii) a group of increased TGFβ/BMP signaling (osteopoikilosis/melorheostosis and Camurati–Engelmann disease), iii) a group of dysregulation of pyrophosphate metabolism (AD craniometaphyseal dysplasia), iv) a group of dysregulation of prostaglandin or thromboxane metabolism (pachydemopriostosis, cranioosteoarthropathy, and Ghosal hematodiaphyseal dysplasia), and v) a heterogeneous group of disorders whose phenotypes are composed of bone changes seen in the disorders cited above, singly or in combination, and a subset of which is termed mixed sclerosisng bone dysplasia.
The clinical and radiological manifestations of these disorders are reviewed, mainly focusing on disorders with abnormal Wnt signaling and increased TGFβ/BMP signaling. Affected individuals have three medical problems. The first is the result of craniofacial hyperostosis (cranial nerve palsy and increased intracranial pressure). The second is painful limbs probably due to cytokine-induction during hyperostotic process. The third includes variable extraskeletal complications (non-progressive myopathy, myelofibrosis, synovitis, and skin changes). Painful limbs may be prominent in a group of increased TGFβ/BMP signaling and sometimes very devastating. Losartan that can suppress TGFβ signaling may be beneficial; yet, its experiences remain anecdotal and sometimes disappointing. New medical intervention is expected.

Disclosure

The author declared no competing interests.

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Biographical details

Dr Gen Nishimura is Radiologist-in-Chief, Department of Pediatric Imaging, Tokyo Meteropolitan Children's Medical Center, Tokyo, Japan. After obtaining the medical degree at Keio University School of Medicine in Tokyo, Dr G Nishimura started his career of diagnostic radiology in the late 1970s. During the exposure to pediatric radiology in early 1980s, he developed a special interest in a diagnosis of skeletal dysplasias. In 1988, he visited Royal Alexandra Hospital for Children in Sydney and learned the subject from Prof. Kazimierz Kozlowski. Thereafter, he was able to develop a number of international scientific collaborations with new friends and mentors, such as Prof. Andrea Superti-Furga in Switzerland and Prof. Juergen Spranger in Germany. He contributed to several new discoveries of disease-causing genes, such as TGFβ in Camurati–Engelmann disease and SLC35D1 in Schneckenbecken dysplasia. He also contributed to recent versions of international nosology and classification of genetic skeletal disorders (2010, 2006 revisions).

IS20

Bone morbidity in children with leukemia

Leanne M Ward

Research Chair in Pediatric Bone Health, Division of Endocrinology and Metabolism, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, Ontario, Canada

Acute lymphoblastic leukemia (ALL) is the most frequent form of childhood malignancy, with a cure rate that now exceeds 80%. As survival improves, the clinical consequences of ALL and its treatment are increasingly recognized, with skeletal health emerging as an important care issue. The skeletal morbidity that arises in this setting falls into two main categories: osteoporosis (low trauma fractures) and osteonecrosis (*in situ* bone death). Osteoporosis and necrosis have the potential to cause acute and chronic bone pain, loss of mobility, and permanent skeletal deformity. These adverse outcomes highlight the deleterious impact of ALL and its treatment on focal and systemic bone metabolism. Up to a third of children with ALL will develop fractures or symptomatic osteonecrosis in the first 5 years. At the same time, recent longitudinal studies have highlighted that most of the bone morbidity occurs in the first 2 years after diagnosis. Vertebral fractures, an important manifestation of osteoporosis in children with leukemia, are frequently asymptomatic and thereby go undetected in the absence of a surveillance programme. On the other hand, vertebral fractures at ALL diagnosis (including mild, asymptomatic vertebral collapse) are among the strongest predictors of future, incident fractures, along with low bone mineral density (BMD) at diagnosis, and higher glucocorticoid exposure. Similarly, osteonecrosis lesions that are evident early in the chemotherapy treatment course (including asymptomatic lesions) predict progression of osteonecrosis at future time points. These important observations highlight the following key concept: understanding the skeletal phenotype early in the child's treatment course (including asymptomatic bone morbidity) is paramount to identifying children at greatest risk for incident fractures and progression of osteonecrotic lesions at subsequent time points.

For most children, leukemia and its related chemotherapy represent transient bone health threats. As such, many children will have the potential for dramatic recovery, including BMD restitution, vertebral body reshaping following fracture, decrease in overall fracture risk, and resolution of osteonecrotic lesions. At the same time, recovery from skeletal morbidity in the leukemia setting is growth-dependent, underscoring the importance of timely diagnosis and appropriate intervention for those who have limited potential for spontaneous vertebral body reshaping and resolution of osteonecrotic lesions due to insufficient residual growth potential.

Different medical interventions have been studied to treat or prevent bone morbidity in children with ALL, including calcium and vitamin D supplementation, calcitriol, and bisphosphonate therapy. Of these, bisphosphonate therapy is associated with the most potent bone-modifying effect, typically reserved for children with osteoporosis and limited potential for spontaneous recovery. Bisphosphonate therapy has also been shown to alleviate pain arising from osteonecrotic lesions; its role in preventing osteonecrosis and its progression is less clear. In older children with advanced osteonecrosis, functional impairment and limited potential for spontaneous recovery, surgical intervention may be warranted.

Disclosure

Receipt of honoraria/consulting fees: Alexion, Novartis.

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Biographical details

Dr Leanne M Ward is an Associate Professor of Pediatrics at the University of Ottawa where she holds a Research Chair in Pediatric Bone Health. She is the Medical Director of the Pediatric Bone Health Clinical and Research Programs at the Children's Hospital of Eastern Ontario (CHEO) and a pediatric endocrinologist within the Division of Endocrinology and Metabolism at CHEO. Dr L M Ward's research program is dedicated to the study of bone development and the treatment of bone disorders in children. She is the principal investigator of the 'STOPP' research program (steroid-induced osteoporosis in the pediatric population), a pan-Canadian project funded by the Canadian Institutes of Health Research to study bone health in children with chronic illnesses. Dr L M Ward has received a number of awards for her work in pediatric bone health, including a Canadian Child Health Clinician Scientist Career Development Award (2004), a Canadian Institutes for Health Research New Investigator Award (2004) and a Canadian Child Health Clinician Scientist Career Enhancement Award (2007).

IS21

Cytokine- and steroid-induced osteoporosis

Sandy Burnham

Division of Rheumatology, Perelman School of Medicine, The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Pediatric inflammatory diseases are associated with low bone mass and fractures during childhood. In conditions such as inflammatory bowel disease and systemic lupus erythematosus, glucocorticoid therapy, and pro-inflammatory cytokines are key factors that impair bone accrual through specific effects on osteoblasts, osteoclasts, and osteocytes. Other factors may contribute to suboptimal skeletal maturation, including malnutrition, pubertal delay, low muscle mass, and physical inactivity. Studies performed in diverse patient populations have documented a greater risk of both appendicular and vertebral compression fractures. Recently, the steroid-induced osteoporosis in the pediatric population (STOPP) study demonstrated that 6% of children with inflammatory diseases receiving chronic glucocorticoid therapy had incident vertebral compression fractures over 1-year of follow up. Those participants with incident vertebral fractures had a greater decrease in lumbar spine aBMD *Z*-scores in the first 6 months. In general, bone strength in the appendicular skeleton is compromised because of thinner cortical bone, with a low periosteal circumference and a normal or expanded endosteal circumference. Low muscle mass likely contributes to, but does not fully account for bone deficits. In children and adolescents with systemic lupus erythematosus have used spine QCT and HR-pQCT to document prominent axial and appendicular bone strength deficits. HR-pQCT trabecular deficits were associated with prevalent vertebral fractures. Despite known effects of chronic inflammatory diseases and concomitant glucocorticoid therapy on bone health and publication of the International Society for Clinical Densitometry Pediatric Position Statement, comprehensive bone health assessments are often not performed as part of routine clinical care. Potential solutions to this implementation gap will be discussed.

Disclosure

The author declared no competing interests.

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Biographical details

Sandy Burnham received his MD from the Perelman School of Medicine at the University of Pennsylvania (UPENN) in 1997 and completed his Pediatrics Residency in 2000 and General Pediatrics and Pediatric Rheumatology Fellowships in 2004 at The Children's Hospital of Philadelphia (CHOP). He received his Master of Science in Clinical Epidemiology from UPENN in 2006. Dr S Burnham is now Associate Professor of Pediatrics at UPENN and practices Pediatric Rheumatology at CHOP, where he is the Pediatric Rheumatology Training Program Director. His research focuses on the impact of chronic inflammatory conditions on skeletal structure using methods such as DXA, pQCT, and spine QCT. Recent work used spine QCT finite element modeling to characterize vertebral strength deficits in children with systemic lupus erythematosus. In addition, Dr S Burnham is interested in developing methods to systematically enhance patient safety and optimize care quality in children exposed to chronic glucocorticoid therapy.

IS22

Anorexia nervosa

Madhusmita Misra

Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

Anorexia nervosa (AN) is reported in 0.2–1% of adolescent girls and is characterized by physiological and adaptive changes in various endocrine axes. Alterations also occur in many hormones secreted or regulated by fat (a reflection of energy stores) that can impact bone. Physiological endocrine changes in AN in turn lead to impaired bone accrual rates, low bone density, impaired bone microarchitecture, decreased bone strength, and an increased risk for fracture. In addition, decreased pubertal bone accrual in AN raises concerns regarding attainment of peak bone mass, an important determinant of bone health and fracture risk in later life. Weight and menses recovery are associated with some improvement in bone accrual, however, residual deficits persist. Therapeutic strategies to improve bone accrual in AN are limited, and include physiologic estrogen replacement in adolescents, and use of bisphosphonates in adults.

Disclosure

The author declared no competing interests.

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Biographical details

Dr Madhusmita Misra is a full Professor of Pediatrics at Harvard Medical School and a Pediatric Endocrinologist at Massachusetts General Hospital in Boston, Massachusetts. She directs the fellowship training program in Pediatric Endocrinology at Massachusetts General Hospital, and has a Masters in Public Health from the Harvard School of Public Health. Dr M Misra's clinical interests include disorders of bone mineral metabolism (including conditions such as anorexia nervosa, the female athlete triad, celiac disease, inflammatory bowel disorders, and autism spectrum disorders), and disorders of growth, puberty, and the pituitary gland. Her past and current research focuses on neuroendocrine and bone changes in conditions that span the nutritional spectrum from anorexia nervosa to the female athlete with amenorrhea to obesity. Her awards include the Janet McArthur Award from Women in Endocrinology and the John Haddad Young Investigator Award from AIMM/ASBMR (amongst others).

IS23

Multiphoton microscopy

Eleonora Dondossola[1] & Peter Friedl[1,2]

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Multiphoton microscopy (MPM) is a powerful approach to visualize live cells and tissues, including bone, in three dimensions and over time. To enable preclinical longitudinal monitoring of bone by intravital MPM we developed an animal window model of bone using existing tissue engineering strategies. Electrospun polycaprolactone scaffolds and human mesenchymal stem cells after osteoblastic differentiation, *in vitro*, were implanted into the mouse skin in the presence of BMP7 to generate a tissue engineered bone construct (TEBC) and characterized by μCT, bone histomorphometry, and histology. After a phase of massive bone deposition and primary remodelling (weeks 1–4), TEBC stabilizes, showing i) consistent cortical thickness, trabecular bone, and bone resident cells and ii) the best cortical thickness/bone cavity ratio compared to other mouse bones, providing optimal optical accessibility.
For intravital multiparameter 3D visualization of the neobone through the body window, MPM excitation was used to co-register the collagenous and mineralized bone matrix (second harmonic, fluorescent-labeled bisphosphonates), adipocytes and bone surface (third harmonics), blood vessels and stromal phagocytes (fluorescence-labeled dextran) and osteoclasts (cathepsin K). Whereas the cortical bone was well-preserved and intact in native bone, co-implantated human prostate cancer cells (PC3) induced reactive remodeling of bone (osteolysis and osteoplastic apposition) together with expansive growth of the lesion.
In conclusion, by combining innovative tissue engineering with optical windows, state-of-the-art fluorescence reporter technology and intravital MPM, integrated analysis of bone formation and remodeling will enhance mechanistic insight into bone physiology and disease.

Disclosure

The authors declared no competing interests.

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Biographical details

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IS24

The new histology

Barbara M Misof

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Additionally to the standard histomorphometric and pathohistologic evaluation, the transiliac bone biopsy sample from a patient can be further analyzed for additional information on structural and material characteristics. Under the term 'new histology', several non-destructive techniques and combinations thereof providing high spatial resolution have been introduced. In contrast to conventional histology, these techniques allow the characterization of structural, compositional as well as mechanical properties of the bone material. At its lowest level of hierarchical structure, bone is a nano-composite consisting of stiff mineral particles embedded in a soft organic matrix. The mineralized collagen fibril represents the basic building block. This level can be accessed by vibrational spectroscopic methods (Fourier Transform Infrared and Raman microspectroscopy). A level of hierarchy higher, these collagen fibrils form fibers in a more or less ordered arrangement (in lamellar or woven bone respectively), which can be described by polarized light microscopy, Raman microspectroscopy and scattering techniques like small-angle X-ray scattering (SAXS). At the microscopic scale of a sectioned sample, the bone structural units with their different mineral content can be visualized and quantified by backscattered electron imaging. The micro-porosity formed by the osteocyte–lacunar–canalicular network can be characterized in 3D by confocal laser scanning microscopy using rhodamine fluorescent stained bone tissue. The characteristics at all these hierarchical levels and their interplay are determinants of the mechanical properties as well as of the intrinsic resistance to fractures. The mechanical material properties can be measured by nano-indentation and acoustic microscopy. All these characteristics of bone provide information for fracture risk assessment and reflect the history of the bone turnover and mineralization processes. The deviations from normal in pathological conditions might contribute to differential diagnosis and support the understanding of pathophysiological mechanisms and the effects of treatment.
The power of these techniques for histologic analysis, which can be complemented by micro-CT regarding architectural quality, will be demonstrated by examples of specific diseases, including osteogenesis imperfecta and chronic kidney disease among others.

Disclosure

The author declared no competing interests.

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Biographical details

Barbara M Misof is Staff Scientist at the Ludwig Boltzmann Institute of Osteology, Vienna, Austria. She completed her PhD in Physics and Postgraduate Education in Medical Physics at the University of Vienna in 2000. In 2002, she received the Herbert-Czitober-Research Award of the Austrian Society of Bone and Mineral Research. Her areas of interest are bone material properties, structure-function relation, effects of osteoporosis treatments with a focus on bone matrix mineralization.

IS25

Beyond the mechanical in muscle–bone interaction

Lynda F Bonewald

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The close relationship between muscle and bone has long been recognized especially during development where one tissue does not develop in the absence of the other. The mechanical interactions between the two tissues have dominated research under the assumption that the major interaction between the two tissues was the loading/unloading of bone by muscle. Though clear that loading of bone by muscle is necessary to maintain healthy bone, the concept that bone could have positive effects on muscle mass and function did not exist until recently. We have shown that bone cells, specifically osteocytes, make factors such as prostaglandin and Wnt3a and unknown factors that support myogenesis and muscle function. We also have data showing that muscle factors can protect osteocytes against cell death or apoptosis due to glucocorticoids or to oxygen radical production and that production of these factors are increased with muscle contraction. Several new *in vivo* studies suggest that bone produces factors that increase and maintain muscle mass in young animals, but that with age, osteocytes actually produce factors that decrease muscle mass and function. For muscle diseases, it will be important to determine if specific bone factors can reduce or ameliorate the disease and conversely, for bone disease, it will be important to identify muscle factors as potential therapeutics.

Disclosure

The author declared no competing interests.

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Biographical details

Dr Lynda F Bonewald is a University of Missouri, Kansas City (UMKC) Curators Professor, the Lefkowitz Professor of Oral and Craniofacial Sciences, and Director of the Mineralized Tissue/Bone Biology Research Program at the UMKC School of Dentistry, Director of the UMKC Center of Excellence in the Study of Dental and Musculoskeletal Tissues and UMKC Vice Chancellor for Clinical and Translational Research. Dr L F Bonewald was educated at the University of Texas, Austin, where she earned a BA in Biology and at the Medical University of South Carolina, Charleston, where she received a PhD in Immunology/Microbiology. She is Past-President of the ASBMR and is best known for her work in the study of osteocyte biology and function.

IS26

Duchenne and cerebral palsy

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Childhood and adolescence are critical periods for optimizing bone growth and mineral accrual. Bone strength is determined by bone size, geometry, quality, and mass – variables that are influenced by genetic factors, physical activity, nutrition, and pubertal hormones. Duchenne muscular dystrophy (DMD) and cerebral palsy (CP) are two chronic medical conditions of childhood associated with reduced mobility and increased rate of pathological fracture. DMD is an X-linked disorder of muscle limited to males. Chronic and progressive immobilization is an inevitable consequence of DMD. Corticosteroids assist in keeping boys with DMD more mobile but also result in inevitable and progressive bone loss and increased fracture risk, both in the axial and appendicular skeleton.[1] Long-bone and vertebral fracture are seen in up to 75 and 30% of boys respectively.[1] Of major concern, as many as 20–50% of boys ambulant prior to the fracture, lose their ability to walk after the fracture[1].

CP is the most common cause of physical disability in childhood with a prevalence of approximately one in 500 children. Mobility and areal bone mineral density (aBMD) decline and fracture risk increases with increasing age in children with CP.[1,5] Costs of care, the burden placed upon families and risk of osteoporotic fracture all increase as immobility increases in CP.[5,6] Bisphosphonates are being administered with increasing frequency to children with secondary osteoporosis.[5] There are a paucity of controlled trials of bisphosphonates in children with DMD or CP. Available data would suggest bisphosphonates increase BMD, but there is little to suggest that they reduce fracture rate. RCTs are currently underway to address this. Novel treatment approaches in DMD and CP include the use of whole body vibration plates, RANKL inhibitors and anti-sclerostin antibodies. Early intervention to maintain mobility is critical in ambulant children with CP.

This presentation will address the mechanism underlying bone fragility in DMD and CP, data on fracture risk and current and future treatment options.

Disclosure

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References

1. McAdam LC, Mayo AL, Alman BA & Biggar WD. The Canadian experience with long-term deflazacort treatment in Duchenne muscular dystrophy. *Acta Myol* 2012 **31** (1) 16–20.

2. Henderson R *et al*. Growth and nutritional status in residential centre versus home-living children and adolescents with quadriplegic cerebral palsy. *J Ped* 2007 **151** (2) p161–p166.

3. Fowler E *et al*. Promotion of physical fitness and prevention of secondary conditions for children with cerebral palsy: APTA Pediatric Research Summit. *Phys Ther* 2007 **87** (11) 1495–1510.

4. Chen C *et al*. Factors associated with bone density in different skeletal regions in children with cerebral palsy of various motor severities. *Develop Med Child Neurol* 2011 **53** 131–136.

5. Simm PJ *et al*. Zoledronic acid improves bone mineral density, reduces bone turnover and improves skeletal architecture over 2 years of treatment in children with secondary osteoporosis. *Bone* 2011 **49** (5) 939–943.

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Biographical details

Associate Professor Craig Munns is a Senior Staff Specialist in Bone and Mineral Medicine and Endocrinology at the Children's Hospital at Westmead and Conjoint Associate Professor in the Sydney Medical School at the University of Sydney, Australia. Following the completion of his Paediatric and Endocrinology training at The Royal Children's Hospital, Brisbane, Australia, Associate Professor C Munns was Clinical Associate in Genetic and Metabolic Bone Disorders at the Shriners Hospital for Children, Montreal, Canada. He was awarded his PhD through the University of Queensland in 2004. Associate Professor C Munns' major clinical and research focus is the diagnosis and management of primary and secondary bone disorders in children.

Oral Communications

OC1

Abnormal trabecular micro-architecture and bone mechanical properties in adolescent idiopathic scoliosis: a case–control study with high-resolution peripheral quantitative computed tomography and finite element analysis

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Adolescent idiopathic scoliosis (AIS) is associated with low bone mineral density (BMD) which has been reported to be an important prognostic factor for curve progression. In addition to BMD, high-resolution peripheral quantitative computed tomography (HR-pQCT) allows measurement of volumetric BMD, bone morphology, trabecular micro-architecture, and evaluation with structure model index (SMI) and finite element analysis (FEA) for mechanical property assessment. The aim of this study was to compare the trabecular micro-architecture configuration and bone mechanical properties between AIS and matched adolescent controls.

101 AIS girls aged 12–14 years and equal number of age and gender-matched normal controls were recruited. Detail anthropometric data, dietary food and standardised physical activities questionnaires were collected. Bilateral femoral necks and non-dominant distal radius were scanned by DXA for areal BMD and HR-pQCT for bone morphology, volumetric BMD, micro-architecture, SMI and FEA respectively. Based on their areal BMD, subjects were classified as osteopenic if the *Z*-score < -1. Bone mechanical properties including stiffness, failure load and apparent modulus were calculated from FEA. Multivariate linear regression model was used to control confounding from age, physical activity level (PA) and dietary calcium intake (Ca).

The mean age of AIS and controls were 12.94 ± 0.66 and 13.06 ± 0.50 years respectively. The mean Cobb angle of the major curve for AIS subjects was $21.5° \pm 6.0°$. AIS was associated with lower failure load and apparent modulus ($\beta = -130.16$ and -141.72, $P = 0.048$ and 0.032) after adjusting for age, and lower apparent modulus ($\beta = -125.70$, $P = 0.046$) after adjusting for age, PA and Ca. Osteopenic AIS was associated with higher SMI when compared with non-osteopenic AIS (%diff = 14.5%, $P < 0.001$) whereas no difference was found between osteopenic and non-osteopenic controls.

AIS girls were associated with deranged trabecular micro-architecture and lower bone biomechanical properties with characteristic SMI profile seen with osteopenia. This might be the result of abnormal regulation and modulation of bone metabolism as well as bone modelling during growth in AIS. Further longitudinal studies to determine the implication of these abnormalities that characterize AIS are warranted.

Disclosure

The authors declared no competing interests.

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OC2

Feature-based recognition of trabecular microstructure using 1.5T magnetic resonance imaging: a new methodology

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Background

Magnetic resonance imaging (MRI) is used clinically to assess bone marrow, muscle and joints. The assessment of cortical and trabecular structure using MRI may provide further insight into the muscle–bone–bone marrow unit. Previous studies using MRI to evaluate microarchitecture are confined to research due to the need for specially adapted coils and navigator software to limit motion artifact. We present a novel statistical method using HRpQCT to determine the accuracy of a clinical 1.5 Tesla (T) MRI in quantifying trabecular microstructure.

Methods

We recruited 96 healthy 13–16 years old to undergo HRpQCT and 1.5T MRI of the non-dominant ultradistal tibia. Participants underwent two of the following axial MRI sequences: T1-weighted Fast Spin Echo (T1w), T2-weighted Fast Spin Echo (T2w), T2*-weighted Gradient Echo (T2*w), FIESTA, Ultrashort Time Echo (UTE), Ultrashort Time Echo High Resolution (UTE-HR). By relating trabecular parameters derived from the HRpQCT images, contextual image features contained within a defined region of interest within low resolution MRI sequences were used to develop a statistical prediction model designed to predict trabecular microstructural parameters. Image descriptors included statistical variability (mean intensity, standard deviation, skewness, and kurtosis), pattern repeatability (using grey level co-occurrence matrices), and pattern complexity (using run-length analysis and fractal dimension). Kernel partial least squares was used to find an optimal non-linear predictor model from the data relating MRI sequences to HRpQCT parameters. Prediction errors for the trabecular indices (trabecular thickness, spacing and number) were determined by using the different MRI sequences as the input of the prediction model.

Results

The FIESTA and UTE-HR image sequences demonstrated the highest accuracy in predicting all three trabecular parameters ($12.01 \pm 3.44\%$, $12.08 \pm 4.48\%$ respectively). T1w provided the highest predictive value in quantifying trabecular spacing (7.42% average error). T2w and T2*w most accurately predicted trabecular thickness (9.51%) and trabecular number (7.51%), respectively. Combining MRI sequences in the model to predict individual trabecular components did not improve the accuracy

Conclusions

Using the established predictive model, 1.5T MRI sequences can predict trabecular number, spacing, and thickness to within 10% of the values derived from HRpQCT. This study demonstrates the future potential of clinical MRI in assessing trabecular bone.

Disclosure

The authors declared no competing interests.

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OC3

Sedentary time negates the positive influence of moderate-to-vigorous physical activity but not vigorous physical activity on bone strength in adolescent girls

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We examined the influence of objectively measured moderate-to-vigorous physical activity (MVPA) and vigorous PA (VPA) and sedentary time (SED) on bone strength, structure and density in post-pubertal girls.

We had 63 healthy girls (15.3 ± 0.3 years) from the Health Promoting Secondary Schools (HPSS) study with valid accelerometry data and tibia scans. We assessed the left tibia using peripheral quantitative computed tomography (pQCT, XCT 3000, Stratec). We derived bone strength index (BSI, mg^2/mm^4), total bone area (Tt.Ar, mm^2) and density (Tt.Dn, mg/cm^3) at the distal tibia (8% of tibial length), and polar strength-strain index (SSIp, mm^3), cortical area (Ct.Ar, mm^2), density (Ct.Dn, mg/cm^3) and thickness (Ct.Th, mm) at the 50% site. We assessed PA objectively using accelerometers (GT1M, Actigraph) and considered accelerometry data valid if participants had a minimum of 3 days, 10 h/day of wear time with non-wear time defined as 60 min of continuous zero counts. We defined SED as ≤ 100 counts/min (cpm), MVPA as ≥ 2296 cpm, and VPA as ≥ 4012 cpm 1. Using nested, multivariable regression models, we examined the influence of SED and PA on bone outcomes; controlling for ethnicity, tibia length, age at menarche and whole body lean mass (by dual-energy X-ray absorptiometry (DXA, Discovery-A, Hologic)). We also controlled for total wear time when we added SED in the models.

Girls had 44.0 ± 20.7 min/day of MVPA and more than 10 h/day of SED (611.7 ± 69.4 min/day). Initially, MVPA explained 6% and 7% of the variance in Tt.Dn and BSI at the distal tibia, respectively ($P < 0.05$). When we added SED to the model, MVPA no longer predicted for Tt.Dn or BSI. In contrast, VPA remained a significant predictor of BSI even after SED was added to the model (4% of the variance; $P < 0.05$). MVPA and VPA were not significant predictors of bone strength, structure or density at the tibial shaft.

There appears to be independent consequences of 'unloading' on the growing skeleton in girls through sedentary behaviours, that cannot be compensated for by MVPA. However participation in more vigorous activities may mitigate the negative influence of these behaviours on bone strength in post-pubertal girls.

Reference

1. Evenson KR, Catellier DJ, Gill K, Ondrak KS & McMurray RG. Calibration of two objective measures of physical activity for children. *J Sports Sci.* 2008 **26** (14):1557–65.

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Disclosure
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OC4

Increased bone matrix mineralization in treatment-naïve children with Crohn's disease

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Background
Crohn's disease (CD) is an inflammatory bowel disease which affects many organ systems including the skeleton. In children with CD, bone mineral density is frequently low. Bone metabolic abnormalities, including lower biochemical measures of bone turnover (NTX) as well as decreased bone formation indices at the tissue level have been reported. The aim of our study was to gain information on the bone matrix mineralization in CD.
Methods
We studied the bone mineralization density distribution (BMDD) based on quantitative backscattered electron imaging (qBEI) in cancellous (Cn.) and cortical (Ct.) compartments from trans-iliac biopsy samples from 20 treatment-naïve children with CD at the time of diagnosis (eight females/12 males, mean age 14.5 ± 2.3 years). The outcomes were compared to healthy reference BMDD data ($n=54$).
Results
The BMDD of the untreated patients with CD was shifted toward higher calcium concentrations compared to normal (Figure). In cancellous bone, we found the most frequent calcium concentration (Cn.CaPeak +2.8%, $P=0.004$) and the portion of highly mineralized bone areas (Cn.CaHigh +52%, $P=0.009$) increased compared to the reference cohort. In cortical bone, indices of mineralization heterogeneity (Ct.CaWidth +17.0%, $P=0.001$) and Ct.CaHigh (+30.4%, $P=0.006$, median comparison) were increased. Significant correlations with serum alkaline phosphatase (ALP) and urinary crosslinked N-telopeptide of type I collagen (NTX) were observed: CaMean (the average calcium concentration), CaPeak and CaHigh were decreased (Spearman rank order correlation coefficients R ranging from −0.69 to −0.47, P value from <0.001 to 0.05), while CaWidth and CaLow (the percentage of low mineralized bone areas) from both cancellous and cortical compartments were high (R from 0.45 to 0.65, $P<0.05$ to $P<0.01$) with increasing levels of ALP and NTX.

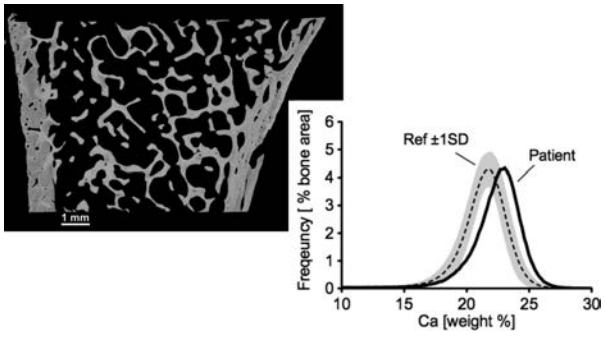

Figure 1

Conclusions
The significant correlations of cancellous and cortical BMDD parameters with ALP and NTX reflect a general dependency of the bone matrix mineralization measured at the iliac crest on bone turnover. The shift toward higher bone matrix mineralization density compared to reference is consistent with the decreased bone formation indices reported for these untreated children with CD.
Disclosure
The authors declared no competing interests.
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OC5

Bivariate analyses of BMD and lean mass in children identifies variants with novel pleiotropic effects across six BMD loci and in the TOM1L2 locus

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Background
Lean and bone mass are heritable traits with high phenotypic correlation ($rho=0.44$), likely reflecting the underlying mechanical and biochemical interactions between tissues.
Aim
Estimate the shared heritability (genetic correlation) of both traits in children and identify genetic determinants displaying pleiotropic effects on lean mass and bone mass accrual.
Methods
Participants make part of two prospective population-based birth cohorts, the Generation R Study (GenR) and the Avon Longitudinal Study of Parents and Children (ALSPAC). GenR children ($n=4.071$) born in Rotterdam, Netherlands are of multiethnic background with mean age = 6.2, SD = 0.37 years. ALSPAC children ($n=4.820$) born in Avon, UK had mean age = 9.9, SD = 0.32 years. Lean mass and BMD were measured with DXA (GE-Lunar iDXA/ Prodigy) and genome-wide genotyping (GenR: Illumina 660K, ALSPAC: Illumina 550K) imputed to HapMap. Shared heritability estimates derived from array data of GenR were obtained using GCTA (with modified admixed-aware relatedness estimates using REAP). GWAS in GenR and ALSPAC were ran using bivariate PLINK. Meta-analysis was performed by Fisher's method. All analyses were adjusted for age, sex, height, fat percent (and 20 genomic principal components in GenR). $P<5\times10^{-8}$ was considered genome-wide significant (GWS).
Results
Heritability estimates were 0.31 for BMD and 0.40 for lean mass, with a genetic correlation of 0.3. The bivariate GWAS meta-analysis identified GWS associations with concordant effects on lean mass and BMD; mapping to six established BMD loci including: *WNT4, GALNT3, CPED1/WNT16, RANKL, RIN3* and *PPP6R3/LRP5*. Another GWS signal mapping to the *TOM1L2* locus, showed opposite correlations between lean mass (−0.46) and BMD (0.59). ENCODE analyses identified enhancers for *SREBF1* in the same haplotype block.
Conclusion
Several variants at BMD loci exert pleiotropic effects on lean mass. Bivariate analysis is a powerful method for identifying novel pleiotropic effects. *SREBF1* is a regulator of muscle protein synthesis down-regulating *MYOD1*, *MYOG* and *MEF2C* factors. Functional studies are required to unravel underlying pleiotropic mechanisms.
Disclosure
The authors declared no competing interests.
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OC6

Early life motor control is positively associated with adolescent bone strength

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Recent evidence supports a strong influence of early life movement on infant bone strength. However, it is not known whether early motor development also influences bone strength in later life. Therefore, we examined relationships between locomotor score (using components of the Denver Developmental Screening Test) at 18 months, and the Avon Longitudinal Study of Parents and Children (ALSPAC) Co-ordination Test (ACT) score at 7 years, and bone outcomes as measured at age 17 years, in 3810 ALSPAC participants. Total hip bone mineral density (BMD) was assessed from dual-energy X-ray absorptiometry (DXA), and periosteal circumference (PC), cortical thickness (CT), cortical bone area (CBA), cortical BMD (BMD_C) and cross sectional moment of inertia

(CSMI) by peripheral quantitative computed tomography (pQCT) at the 66% tibial site. Positive relationships were observed between 18 month and 7 year motor scores, and hip BMD (0.075 (0.072, 0.078) and 0.088 (0.053, 0.124)), PC (0.085 (0.016, 1.108) and 0.056 (0.030, 0.083)), CT (0.089 (0.061, 0.118) and 0.050 (0.020, 0.081)), CBA (0.098 (0.074, 0.123) and 0.064 (0.036, 0.092)) and CSMI (0.098 (0.059, 0.105) and 0.065 (0.039, 0.092)) (standardized beta coefficients (95% CI) for associations with 18 month and 7 year motor development score respectively, adjusted for sex, age at exposure/outcome, maternal social class, birthweight and gestation age ($P<0.001$ for all associations)). Equivalent associations were not seen for BMD_C ($P=0.52$ and 0.22 for locomotor and ACT score respectively). Gender×motor score interactions were observed for hip BMD and tibia CA and CSMI (all $P<0.01$) with regression coefficients greater in males. In further analyses intended to explore the role of body composition in mediating these relationships, positive associations with hip BMD and pQCT parameters were attenuated by adjustment for height, fat and lean mass at 17 years (36–82% reduction). In conclusion, early life motor development is positively related to skeletal development as measured at age 17, particularly in boys, reflecting both greater periosteal expansion and reduced endosteal expansion, resulting in greater predicted bone strength. Changes in body composition may play a role in mediating these relationships between early motor development and subsequent bone development, possibly reflecting altered levels of physical activity.

Disclosure

The authors declared no competing interests.

DOI: 10.1530/boneabs.4.OC6

OC7

Osteogenesis imperfecta: a pilot trial on treatment with the RANKL-antibody denosumab

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Osteogenesis imperfecta is a rare disease leading to multiple fractures, skeletal deformities and scoliosis due to a reduced bone mass. Pathological fractures caused by inadequate traumata are the most severe symptom. More than 85% of patients are affected by mutations in COL1A1/A2 impairing quantity and quality of collagen. At present no approved drugs for OI treatment in childhood are available. A single centre prospective pilot study was performed to assess safety and efficacy of an antiresorptive therapy with the RANKL-antibody denosumab in children 5–10 years with OI caused by mutations in COL1A1/A2.

10 children (male $n=7$, mean age of 7.48 years) with genetically confirmed OI (COL1A1: seven patients) were included. All children were treated at least 2 years with neridronate before trial entry. Denosumab was applicated after a washout phase of at least 6 months every 3 months with 1 mg/kg body weight s.c. for 1 year. Weight adjusted vitamin D and calcium substitution was given 4 weeks after each application. Primary efficacy endpoint was change of areal bone mineral density at the lumbar spine assessed by GE lunar iDXA. Mobility was evaluated by gross motor function measurement (GMFM-88) and 1-min walking test if applicable. Bone metabolism markers were evaluated in serum and urine before and between applications for safety monitoring.

8 out of 10 children completed the trial yet (database closure February 2015). After 40 applications of denosumab no severe side effects were observed. A slight hypocalcemia without clinical relevance was seen in all children within the first days after application.

DXA assessment showed a mean increase of lumbar spine Z-scores of +0.9 SD ($n=8$) and total body less head Z-scores of +0.6. Mobility improved in all children (mean percent change of: GMFM-88=3.1% ($n=8$); 1-min walking distance=20.1% ($n=6$)).

Based on our preliminary results denosumab is effective to reduce bone resorption and increase bone mineral density in children with classical OI. Denosumab seems to be safe in the short-term application at least if a close monitoring/substitution of calcium is guaranteed. Finally, long-term observation and a higher sample size are essential to assess risk–benefit ratio more detailed.

Disclosure

The authors declared no competing interests.

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OC8

Combination sclerostin antibody and zoledronic acid treatment outperforms either treatment alone in a mouse model of osteogenesis imperfecta

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Introduction

Bisphosphonate treatment in children with osteogenesis imperfecta reduces bone catabolism and relies on modelling to form new bone. An anabolic treatment, anti-sclerostin antibody (Anti-SOST Ab), is being investigated in clinical trials. We hypothesized that combined treatment may produce superior outcomes in OI.

Methods

Female Col1a2 G610C mice and their wild type littermates (WT) were treated from week 5 to week 9 of life with either saline (control), zoledronic acid (ZA) 0.025 mg/kg s.c. weekly, Anti-SOST Ab given 50 mg/kg i.v. weekly (Anti-SOST), or a combination of both (ZA Anti-SOST). Outcomes included weekly DEXA for areal bone mineral density (BMD) (GE Lunar PIXImus WI, USA), μCT (SkyScan 1174 Kontich, Belgium), mechanical testing of tibiae in four point bending (Instron 5944, MA, USA). Data were analysed with one-way ANOVA (SPSS v11).

Results

Increases in tibial BMD were seen over time in all groups. Anti-SOST treatment alone had no effect on tibial BMD, while ZA (16%) and ZA Anti-SOST (27%) treatments produced significant increases from weeks 1 to 4 ($P<0.05$). μCT analysis showed increases in tissue mineral density and cortical thickness for combined treatment over respective controls. Tibial four-point bending showed only combined ZA Anti-SOST yielded a significant increase in strength and energy to failure in OI mice, restoring bone strength to that of untreated WT mice. In the spine, all treatments increased compression strength over control, Anti-SOST 30%, ZA 43% and ZA Anti-SOST 91% ($P<0.05$).

Discussion

Anti-SOST Ab alone had effects on trabecular but not cortical sites in this study in Col1a2 G610C mice. Roschger *et al*. reported minimal effect in the Col1a1(Jrt)/+ mouse model treated with Anti SOST Ab, whereas large effects were noted with just 2 weeks treatment in 8 week-old Brtl/+ mice, leading to increase in bone size and strength.

Conclusion

A combination of zoledronic acid and anti-sclerostin antibody is superior over either treatment alone in the Col1a2 G610C model of OI. Further studies are required in alternate mouse models of OI to confirm efficacy across different models, and thus to predict possible efficacy across the heterogeneous population of OI patients.

Disclosure:

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OC9

Skeletal manifestations in pediatric WNT1 osteoporosis

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Objectives

We recently identified a heterozygous missense mutation c.652T→G (p. C218G) in *WNT1* as the cause of severe primary osteoporosis (Laine *et al*. *New Engl J Med* 2013). The mutated WNT1 reduces activation of the canonical WNT1/β-catenin-signaling, resulting in decreased osteoblastic function. The mutation was originally identified in a large Finnish family presenting with dominantly inherited, early-onset osteoporosis, with affected adult patients showing reduced bone mineral density (BMD) and high incidence of vertebral compression fractures. The objective of this study was to examine skeletal phenotypes and possible progression with age in mutation-positive pediatric patients.

Methods
This study included six subjects below the age of 18 years who were found to harbor the heterozygous p. C218G *WNT1* mutation, as confirmed by Sanger sequencing. Medical records were reviewed for fractures, medications and possible other illnesses. DXA and radiographic imaging were used to evaluate BMD and skeletal phenotypes. Peripheral blood and urine samples were obtained to exclude secondary causes and to assess calcium, phosphate and vitamin D levels.
Results
The six patients, three girls and three boys, ranged in age from 12 to 17 years, and had normal growth. Childhood low-energy fractures were common. All patients had BMD *Z*-scores below the normal mean, and there was a clear progression of loss in BMD with age. Radiographs revealed loss in vertebral height, osteopenic appearance and in three patients, abnormally thin fibulae and overtubulation of tibiae. Blood and urine samples showed no abnormalities in calcium, phosphate or vitamin D levels; bone turnover markers were normal.
Conclusions
This study confirms that skeletal changes in dominantly inherited *WNT1* osteoporosis are established already at early childhood and progress with age. Early intervention and possible treatment could significantly improve bone health in affected individuals and prevent severe fractures. In light of these results genetic testing of children to affected parents is recommended. Optimal treatment of *WNT1* osteoporosis in children remains to be established in future clinical studies.
Disclosure
The authors declared no competing interests.
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OC10

Lack of PEDF within the bone matrix is associated with osteoidosis and abnormally high bone mineral content

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Background and methods
Pigment epithelium-derived factor (PEDF) is a potent antiangiogenic factor, ubiquitously expressed and secreted in human tissues. Hypertrophic cartilage and osteoblasts express PEDF that binds to type I collagen and glycosaminoglycans in the extracellular matrix. Two rare forms of osteogenesis imperfecta (OI) with intact collagen synthesis are associated with PEDF deficiency. Histological observations revealed excessive osteoid formation and prolonged mineralization lag time, suggesting a distinctive mineralization defect. The goal of this study was to characterize the mineralization pattern in bone with deficient PEDF secretion. We used quantitative backscattered electron imaging (qBEI) to assess bone mineralization density distribution in transiliac biopsies from nine children with *SERPINF1* mutations causing PEDF loss-of-function (OI type VI)* and in two biopsies (obtained at the ages of 7 and 25 years) from a patient with a novel mutation in *IFITM5* (p.S40L substitution, atypical type VI OI) encoding BRIL, a transmembrane protein enriched in osteoblasts during mineralization. This patient has normal PEDF serum level but severely decreased PEDF secretion in osteoblasts. We further characterized bone tissue by high-resolution back-scattered electron imaging (hrBEI) and measured thickness, shape and arrangement of mineral particles by synchrotron small-angle X-ray scattering (SAXS) in a subset of patients with *SERPINF1* mutations.
Results
qBEI revealed hypermineralized bone matrix in all cases, with a similarly increased typical calcium content, coexisting with areas having unusually lower mineral content than controls and OI patients with collagen-gene mutations. In bone with the *IFITM5* mutation we found in the childhood biopsy accumulation of highly mineralized non-remodeled bone. In the young adult biopsy, most bone appears remodeled although average mineral content was still highly increased. HrBEI showed high density of oddly shaped lacunae from young osteocytes with abnormal collagen fibril organization in the perilacunar regions. SAXS revealed smaller mineral particles with a less ordered arrangement than age-matched controls and OI with collagen-gene mutations.
In conclusion, our data suggest that local deficiency of PEDF within the bone matrix impairs the early steps of mineralization at the onset of osteoblast–osteocyte differentiation, resulting in the previously undescribed occurrence of abnormally highly mineralized bone matrix coexisting with extended regions of poorly mineralized bone.
*BONE, in press
Disclosure
The authors declared no competing interests.
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OC11

Comparison of RANKL blockade and bisphosphonate anti-resorptive therapies in a growing mouse model of OI: implications of prolonged treatment on bone health

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Objective
The purpose of this ongoing study was to determine whether osteogenesis imperfecta (OI) patients entering adulthood should continue with bisphosphonate therapy or would benefit from switching to a RANKL blockade therapy. To address this question, we used a mouse model of type-III OI.
Methods
Under IACUC-approval, +/+ and *oim/oim* mice were treated from 2–26 weeks ($n=20$/treatment/genotype) with either 1) saline 24 weeks; 2) saline 12 weeks then RANK-Fc 12 weeks (saline+RANK-Fc); 3) RANK-Fc 24 weeks; 4) ALN 12 weeks then RANK-Fc 12 weeks; or 5) ALN 24 weeks (ALN: 0.21 mg/kg per dose; RANK-Fc 1.5 mg/kg per dose). Groups 3, 4, 5 defined as long-term treatment. Animals were faxitroned at 14 and 26 weeks; fractures were counted in all long bones and five vertebrae into the tail. Femurs and humeri were scanned and evaluated using micro-computed tomography (μCT) and were mechanically tested by three-point bending. Demineralized femurs and tibias were evaluated histologically. Statistics: mixed linear model adjusted for body size; $P<0.05$ considered significant.
Results
All treatments reduced fracture incidence at 14 and 26 weeks. From 14 to 26 weeks no new fractures occurred in the long-term treatment groups; saline-treated mice averaged 0.9 new fractures and saline+RANK-Fc averaged 0.3 new fractures.
Biomechanics
Saline-treated +/+ mice sustained higher loads, were more ductile, and had a greater work-to-fracture compared to *oim/oim* mice. Long-term treated +/+ bones were more brittle compared to saline-treatment. No changes were found in *oim/oim* mice.
μCT
Saline-treated +/+ had greater cortical BV/TV compared to *oim/oim*. *oim/oim* long-term treatment increased cortical BV/TV compared to saline-treatment. Trabecular bone mass increased with long-term treatment in +/+ and *oim/oim* mice due to increased trabecular number and decreased separation.
Conclusion
Both anti-resorptives, in succession or alone, significantly reduced fracture incidence but did not improve mechanical properties in *oim/oim*. Cortical gains observed by μCT did not correct *oim/oim* values to +/+. All mechanical improvements in +/+ mice were at the expense of brittleness. The anti-resorptive therapies mainly affected trabecular bone mass in *oim/oim*, which was not verifiable by three-point bending. Based on observations at the tissue level, reduction in fracture incidence is likely due to enhanced bone mass and corticalization of trabecular bone, an effect that was not sex-, genotype-, or treatment-specific.
Disclosure
We received drug and money for this study from Amgen. Dr Boskey owns stock in Amgen. Dr Raggio sits on the medical board for the Osteogenesis Imperfecta Foundation.
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OC12

A zebrafish osteogenesis imperfecta model: a new tool to develop novel pharmacological treatments

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Objectives
Osteogenesis imperfecta (OI) is a bone disease mainly caused by collagen type I mutations and characterized by bone fragility. No definitive cure is available and the search for novel treatments is necessary. The small teleost *D. rerio* is particularly appealing for drug screening approaches. A zebrafish OI model (*Chihuahua*) carrying in heterozygosis the G574D substitution in the α1 chain of collagen type I is available. To use this model for drug tests it is mandatory to understand the composition of collagen type I, since three genes coding for three different α(I) chains have been described, but their stoichiometry is still unknown.
Methods
Collagen I was extracted from skin, scales and bone of WT and *Chihuahua* adult fishes and from embryos, and separated by 1D and 2D SDS-PAGE followed by mass spectrometry. Amino acid analysis and Differential Scanning Calorimetry were performed, such as RT-PCR for collagen genes. Skeleton was analyzed by X-ray, microCT, alizarin red/alcian blue and calcein staining. Electron microscopy of osteoblasts was performed.
Results
Electrophoretic analysis followed by mass spectrometry revealed in adults the comigration of α1 and α3 chains in a unique band/spot, while in embryos it was possible to distinguish an α1 and an α1/ α3 comigrating band. The α2 band was always separated and in the classical 1:2 ratio respect with α1 and α3 bands. These data and the amino acid analysis suggest the existence of $[\alpha1(I)]_2\alpha2(I)$ and α1(I) α2(I) α3(I) heterotrimers in embryos and of α1(I)α2(I)α3(I) in adults. The Tm for bone, scales and skin collagen was similar. SDS-PAGE showed overmodification of the mutant collagen I compared to WT. X-ray and microCT revealed severe skeletal deformities, multiple bone fractures and reduced mineralization in adult *Chihuahua* fishes, while skeletal staining demonstrated a delayed mineralization in embryos. The presence of ER cisternae enlargement in osteoblasts was evident by electron microscopy analysis.
Conclusion
The collagen composition in embryos and adult fishes is different. The collagen overmodification and ER retention, the skeletal deformities and abnormal mineralization found in *Chihuahua* reproduce the main features reported in OI patients, validating this model for the study of the disease and to evaluate novel possible target for OI treatment.
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Disclosure
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OC13

Meclozine has a potential effects on short stature and foramen magnum stenosis in transgenic mice with achondroplasia

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ACH (achondroplasia) is one of the most common skeletal dysplasias with severe short stature caused by gain-of-function mutations in the FGFR3 gene. Foramen magnum stenosis is a serious neurological complication of ACH. Downregulation of the FGFR3 signaling is a radical therapeutic strategy for the disease. We previously demonstrated that meclozine, an over-the-counter drug for motion sickness, inhibited elevated FGFR3 signaling in chondrocytic cell lines. In the present study, we investigated the effects of meclozine on longitudinal bone growth and foramen magnum stenosis in transgenic ACH mice.

We used transgenic mice carrying the heterozygous $Fgfr3^{ach}$ transgene. Food containing meclozine (0.4 g/kg) was administered to growing $Fgfr3^{ach}$ mice for three weeks and analyzed by micro-computed tomography scans. The bone length and the area of foramen magnum were calculated using reconstructed 3D images. For histological evaluation of the cranial base in newborn infants, the meclozine food was administrated to pregnant mice carrying $Fgfr3^{ach}$ embryos after 14 days of gestation. Complete and uncompleted bony bridges of the spheno-occiping synchondrosis and anterior intraoccipital synchondrosis were scored at two and one points, respectively.
The bone lengths including the radius, ulna, femur, tibia, and vertebrae (L1-5) in the meclozine-treated $Fgfr3^{ach}$ mice were significantly longer than those in the untreated $Fgfr3^{ach}$ mice. Foramen magnum areas, however, showed no significantly differences between the mutant mice with and without meclozine treatment. The bony bridges of synchondroses around foramen magnum were commonly found in $Fgfr3^{ach}$ mice at postnatal 5 days without treatment, but meclozine significantly decreased the bony bridge score (Figure).
Meclozine promoted longitudinal bone growth in growing $Fgfr3^{ach}$ mice. Maternal administration of meclozine could prevent premature closure of synchondroses around foramen magnum in $Fgfr3^{ach}$ mice.

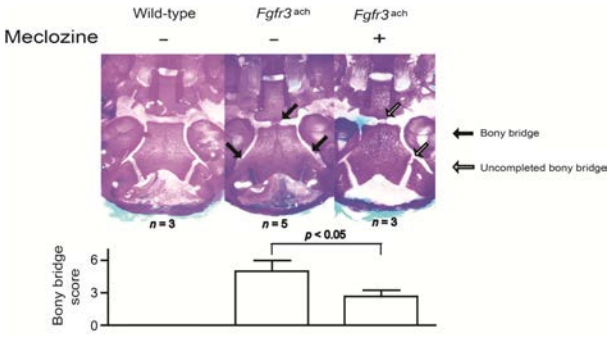

Figure 1

Disclosure
The authors declared no competing interests.
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OC14

Small interfering RNAs as an innovative therapeutic approach for the autosomal dominant osteopetrosis type 2 (ADO2)

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Autosomal dominant osteopetrosis type 2 (ADO2) is a rare genetic disease due to reduced osteoclast function. Clinical manifestations are variable, and in some cases the symptoms, including frequent fractures, osteomyelitis, hematologic and neural failures, are already evident during childhood and worsen with age. In 70% of cases, ADO2 is caused by heterozygous dominant negative mutations of the CLCN7 gene, encoding the Cl−/H+ antiporter type 7. We hypothesized that silencing the mutant CLCN7 transcript by small interfering (si)RNA could rescue the normal phenotype, and tested this hypothesis in the first animal model for this disease: the mouse harbouring the heterozygous Clcn7G213R mutation (ADO2 mice), recently developed by our group. We used a mutation-driven strategy to design and test *in vitro* various siRNAs against this mutation, finding a siRNA that specifically silenced the mutant transcript in the Clcn7G213R-transfected HEK293 cells (−85%, $P=0.02$), without affecting the WT allele. Of note, treatment with the Clcn7G213R-siRNA, rescued the *in vitro* bone resorption in ADO2 mice osteoclasts (+2.6-fold, $P=0.003$). This siRNA was conjugated with the delivery reagent '*in-vivo*-JetPEI' and injected i.p. in ADO2 mice. Pharmacodynamic experiments evidenced 4 mg/kg every 48 h to be the most effective treatment regimen, strongly decreasing the mutant mRNA in tibias of treated mice (−80%, $P=0.01$). Consistently, 2-weeks treatment down-regulated Clcn7G213R mRNA in bone and other organs, increased the serum bone resorption marker CTX over the osteoclast marker TRAcP 5b (+1.8-fold, $P=0.002$), and decreased trabecular BV/TV (−19%, $P=0.04$) and Tb.N

(−16%, $P=0.05$) vs scrambled-siRNA treated ADO2 mice. After 4 weeks, trabecular BV/TV (−21%, $P=0.03$) and trabecular variables (Tb.N −19%, Tb.Sp +1.2-fold, $P<0.03$) returned to WT level, with a full rescue of the bone phenotype. In the rescued ADO2 mice, serum CTX/TRAcP, osteoclast number and erosion surface/bone surface were normalized (+1.2-fold, −32%, +2.1-fold, $P=0.03$, $P=0.01$, $P=0.02$, respectively, vs control ADO2 mice), while osteoblast and dynamic parameters were unremarkable. Treatment was well tolerated, with no adverse events, and with normalization of liver aspartate aminotransferase. To the best of our knowledge, this is the first experimental curative treatment of ADO2, which rescued osteoclast function and returned the bone phenotype to normal. The invention is protected by the patent application RM2014A000272.

Disclosure

The authors declared no competing interests.

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OC15

Osseous side effects on the growing skeleton exerted by tyrosine kinase inhibitor treatment: data observed in pediatric patients with chronic myeloid leukemia in comparison to a juvenile rat model

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Background

The tyrosine kinase inhibitor (TKI) imatinib is applied as front-line treatment in adult and pediatric patients with chronic myeloid leukemia (CML) in order to selectively inhibit the causative oncogenic BCR-ABL1 tyrosine kinase. However, TKIs exhibit off-target effects on further kinases involved in the regulation of bone metabolism. As consequence, pediatric patients display longitudinal growth retardation while on imatinib treatment. As CML is a rare disease in children, growth experiences are limited so far (Millot F 2009 Blood; Shima H 2011 Pediatrics). Therefore, we examined longitudinal growth in a pediatric CML cohort and also established a juvenile rat model to investigate side effects of long-term TKI exposure on the growing skeleton.

Methods

102 CML patients (54♂/48♀) receiving upfront imatinib were enrolled in growth analysis using height SDS. The animal model comprises male Wistar rats which starting at the age of 4 weeks (w) were continuously or intermittently exposed to TKI at varying dosages over 10w. After defined time intervals of exposure (after 2w, prepubertal stage; 4w, pubertal stage; 10w, postpubertal stage, respectively), rats were sacrificed and bone parameters and osseous metabolism were investigated.

Results

A mean decrease in height of 0.48 SDS per year (y) during the first 2 years of imatinib treatment was observed, with prepubertal patients being more severely affected (−0.75 SDS/y) compared to pubertal teenagers (−0.02 SDS/y). The juvenile animal model demonstrated altered osseous parameters (bone length, trabecular BMD, bone strength) predominantly in long bones compared to vertebrae. Dose-dependently decreased osteocalcin- and TRAP-serum levels were observed. Intermittent treatment minimized osseous and biochemical changes.

Conclusion

Growth retardation is a significant adverse effect of TKI treatment in pediatric patients, which could be uniformly modeled in juvenile rats. In addition, high-dose, long-term TKI exposure in rats predicts an increased fracture risk. Skeletal side effects were reduced by intermittent treatment thus possibly reflecting a new therapeutic option. Ongoing investigations on next-generation TKI revealed identical osseous alterations with dasatinib, whereas bosutinib exhibited milder changes. Presently, TKI administration is considered a life-long treatment thus requiring regular monitoring of skeletal side effects under long-term exposure.

Acknowledgement

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Disclosure

The authors declared no competing interests.

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OC16

Medicarpin, a natural pterocarpan, enhances bone regeneration in cortical bone defect model by activation of notch and Wnt canonical signalling pathway

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Bone regeneration and fracture healing processes are impaired in post menopausal osteoporosis which is induced by estrogen deficiency. Though agents like BMPs and PTH have been shown to promote bone regeneration but are associated with undesirable side effects. There is a need for new agents that enhance bone regeneration and repair.

The aim of this study was to evaluate the bone regenerative capacity of medicarpin in the osteoporotic rat model. Cortical bone defect was generated by a drill hole injury in femoral bones of adult osteopenic Sprague–Dawley rats. The treatment of medicarpin (at doses of 0.5, 1.0 and 5.0 mg/kg per day)was commenced the day after and continued for 15 days. PTH (10.0 μg/kg per day) was taken as a reference standard. Fifteen days post-treatment, the animals were sacrificed. Bones were collected for static and dynamic histomorphometry at the injury site by confocal microscopy and micro-computed tomography (μCT). RNA and protein from newly generated bone was harvested from the area adjoining the injury site. Using μCT and confocal microscopy it was found that medicarpin promotes bone healing at the injury site and was comparable to PTH in many aspects. Investigation by qPCR and protein expression studies indicated the up regulation of Notch and Wnt signalling components via increased expression of NICD, JAGGED-1, β-catenin and LRP5. Medicarpin treated group also showed predominant immunolocalization of β-catenin at injury site.

In conclusion, our data shows that medicarpin treatment repairs cortical bone defect by activating Notch and Wnt/canonical signalling pathway. These results are also suggestive of its promising role in fracture repair process.

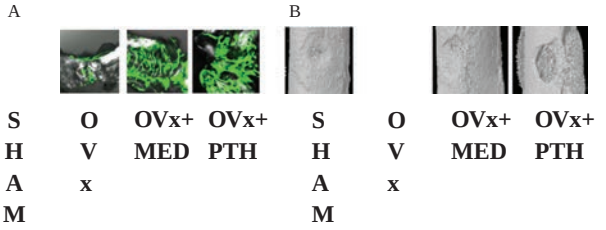

Figure 1 (A) Confocal imaging of fracture callus. (B) MicroCT data of fracture callus.

Disclosure

The authors declared no competing interests.

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OC17

Inhibition of TGFβ signalling delays ossification in patients with fibrodysplasia ossificans progressiva

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Fibrodysplasia ossificans progressiva (FOP) is a rare congenital disorder characterized by progressive heterotopic ossification. FOP patients only present great toe malformations at birth. However, as they grow older they develop soft tissue lumps as a result of flare-ups causing the irreversible replacement of skeletal muscle tissue with bone tissue leading to cumulative physical immobility. Classical FOP patients possess a mutation (c.617G>A; R206H) in the activin receptor IA (ACVR1)-encoding gene which is associated with dysregulated bone morphogenetic protein (BMP) signalling. Nonetheless, not all FOP patients with this mutation exhibit equal severity in symptom presentation or disease progression which indicates a strong contribution by environmental factors. Although inflammation is known to be the main trigger of flare-ups the molecular pathway remains largely unknown.

Our objective was to study the process of osteogenic differentiation in primary dermal fibroblasts from five FOP patients based on a novel method of growth factor-induced osteogenic transdifferentiation. In all patients the presence of the classical FOP mutation was confirmed. The osteogenic properties of the cells

were evaluated by the mRNA expression of Runt-related transcription factor 2 (Runx2), alkaline phosphatase (Alp), osteocalcin (OC) and the presence of mineralization by alizarin red staining. Given the pro-inflammatory role of TGFβ, we also performed pharmacological inhibition of TGFβ signalling by the TGFβ type I receptor inhibitor GW788388.

During osteogenic trans differentiation the expression of Runx2 and Alp over time was higher in FOP cell lines compared to healthy controls (Runx2:$p = 0.001$; Alp:$p > 0.05$). All cell lines exhibited increase in mineralization. Addition of the TGFβ type I receptor inhibitor to the osteogenic media resulted in the attenuation of osteogenic differentiation shown by the decrease in expression of osteogenic markers in patients vs untreated cells at several time points (Runx2:$p = 0.045$). Mineralisation was also inhibited by this inhibitor.

These data indicate that TGFβ is involved in the molecular pathway of flare-up-induced ossification. Inhibition of this pathway may limit ectopic ossification in FOP.

Disclosure

The authors declared no competing interests.

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OC18

Improvement in bone manifestations and respiratory status in infants and young children with HPP treated with asfotase alfa: an update on the ENB-010-10 trial

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Objectives

Hypophosphatasia (HPP) is a rare metabolic disease caused by loss-of-function mutation(s) in the gene encoding tissue-nonspecific alkaline phosphatase (TNSALP). HPP in infants is characterized by poor skeletal mineralization, respiratory compromise, and a high risk of mortality. We previously reported improved mineralization and respiratory function in 15 patients enrolled in this second study of asfotase alfa, a bone-targeted recombinant human TNSALP, in infants and young children.[1] Here we update this information with data from longer follow-up ($\leq$120 weeks) and additional patients (total $n = 28$).

Methods

Study ENB-010-10 is an ongoing multinational, Phase II, open-label trial of asfotase alfa (SC, 6 mg/kg per week; adjustments permitted) in patients $\leq$5 years old with HPP onset $<$6 months. The primary endpoint is change in bone manifestations of HPP at Week 24 (data imputation applied), assessed using a 7-point Radiographic Global Impression of Change (RGI-C) scale (-3=severe worsening; $+3$=complete healing). Other evaluations include respiratory status and safety. Data are reported as median (min, max).

Results

Twenty-eight patients (57% female, age 66.9 (0.1, 309.9) weeks) were included in this interim analysis: 27 and 15 patients were treated $\geq$3 and $\geq$12 months, respectively (duration: 393 (3, 1199) days); one patient withdrew (encephalopathy considered unrelated to treatment). Two patients died (respiratory compromise considered unrelated to treatment). RGI-C score improved with $+1.7$ ($-1.7, +3.0$; $P < 0.0001$; $n = 28$) at 24 weeks, $+2.0$ ($0, +3.0$; $P < 0.0001$; $n = 19$) at 48 weeks, and $+2.5$ ($+1.7, +3.0$; $P = 0.002$; $n = 10$) at 120 weeks of treatment. Twelve (43%) patients did not require respiratory support at any time. Of 16 patients who required support (12 at baseline): five no longer required support and three improved their respiratory status at last assessment. The most common treatment-related adverse events were mild-to-moderate injection-site reactions (180 events/15 patients). Three serious adverse events were considered possibly related to treatment (injection-associated chills and pyrexia: one patient; pneumonia: one patient).

Conclusions

Infants and young children with HPP treated with asfotase alfa experienced improvement in bone manifestations and respiratory function, sustained through up to 120 weeks of treatment. This study further supports the efficacy and safety of asfotase alfa in this population.

References

1. Rockman-Greenberg Horm Res Paediatr 2013 80 (Suppl 1)

Disclosure:

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OC19

The VINE study: vitamin D in newborns: a randomized controlled trial comparing daily and bolus supplementation in breastfed infants of vitamin D deficient mothers

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Objective

There is no published data to demonstrate the efficacy and safety of a single bolus dose vitamin D in breastfed infants of vitamin D deficient mothers. We evaluated the efficacy and safety of this alternative approach in newborn infants $<$4 months of age.

Method

This single centre study was conducted from Aug 2013 to May 2014. Of 307 pregnant women diagnosed with vitamin D deficiency (25OHD$<$50 nmol/l) 70 were recruited. Their newborn infants were randomly assigned a daily dosing of 400 IU vitamin D for 4 months or a single dosing of 50 000 IU cholecalciferol. The primary objective was to ascertain which treatment was more effective in achieving repletion (25OHD$>$50 nmol/l) at 1–2 weeks and 3–4 months. The secondary objective was to determine safety using corrected calcium.

Results

Of 70 eligible infants, 36 received daily low dose and 34 received single high dose cholecalciferol. The mean vitamin D_3 in the bolus group (154 nmol/l, 95% CI 131 to 177) was significantly higher than the daily group (48 nmol/l, 95% CI 42 to 54) ($P < 0.001$) at 1–2 weeks of age, however the reverse was seen at 3–4 months (65 nmol/l, 95% CI 59 to 71) compared to the daily group (81 nmol/l, 95% CI 77 to 85) ($P < 0.008$). Significantly more (100%) infants in the single bolus group achieved vitamin D replete status compared to the daily group at 1–2 weeks (31%) ($P < 0.001$). By 3–4 months, both groups achieved similar vitamin D repletion status (daily 90.9% vs bolus 88.5%) ($P = 0.782$).

Mean corrected calcium levels in the bolus group were within the normal range at 1–2 weeks (daily 2.81 mmol/l vs bolus 2.73 mmol/l) ($P = 0.005$) and 3–4 months (daily 2.58 mmol/l vs bolus 2.55 mmol/l) ($P = 0.242$) despite one-third to half changing from exclusive breastfeeding to mixed and exclusive formula feeding. Clinical parameters for vitamin D deficiency between both groups were similar.

Conclusion

Single bolus dosing of 50,000IU cholecalciferol achieves higher repletion rates of vitamin D_3 at 1–2 weeks compared to daily dosing, although these were similar by 3–4 months. Single bolus dosing did not cause significant hypercalcaemia in the first 3–4 months of life.

Disclosure

The authors declared no competing interests.

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OC20

The effect of calcium supplementation on adolescent bone growth in pre-pubertal Gambian females: a 12-year follow-up study

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In rural Gambian prepubertal children with low calcium intakes (mean 300 mg/day) we reported positive effects, sustained for at least a year (y), on bone mineral content (BMC) after 12 months supplementation with calcium carbonate to international levels[1,2]. The group was followed up regularly until the end of height growth, and supplementation did not affect height growth in the girls[3]. Our

aim was to determine whether the supplementation altered the timing of skeletal growth and mineral accretion, based on the age at peak velocity (APV).
The trial involved 80 girls (8.0–11.9y) randomised to Ca (1000 mg/day, 5-days/week for 1y) or placebo (P), and followed up for 13y. DXA scans and anthropometry were performed 1y and 2y post-supplement and biennially until age 19 when measurements were taken at 1–2y intervals. Outcomes were whole body (WB) and lumbar spine (LS) BMC and bone area (BA), and lean mass. Within-individual changes over time and the effects of supplementation on the longitudinal profiles were analysed by the Superimposition by Translation and Rotation method[4]. Results for APV are presented as mean difference (SEM) (months(mo)).
For the whole group mean APV was: lean mass 13.6y, WBBA 13.8y, LSBA 13.9y, LSBMC 14.4y, WBBMC 14.7y. Comparing the Ca and P groups, APV was earlier at all sites in the Ca group, but not significantly so (WBBMC 0.9 (0.4) mo; WBBA 0.4 (3.6) mo; LSBMC 0.6 (2.4) mo; LSBA 0.7 (2.2) mo).
A year of pre-pubertal Ca supplementation in Gambian girls accustomed to a low calcium intake had no sustained effects on the timing of skeletal growth and mineral accretion. These results mirror those for height growth,[3] and are in contrast to our findings in boys where mean APV in the Ca group was significantly earlier than in the P group[5]. The mechanisms underlying this apparent sexual dimorphism in response to supplementation require further study.
1. Dibba *et al. Am J Clin Nutr* 2000 **71**
2. Dibba *et al. Am J Clin Nutr* 2002 **76**
3. Prentice *et al. Am J Clin Nutr* 2012 **96**
4. Cole *et al. Int J Epidemiol* 2010 **39**
5. Ward *et al. J Clin Endocrinol Metab* 2014 **99**(9)
Disclosure
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OC21

Maternal vitamin D deficiency alters later skeletal responsiveness to mechanical loading in a model system
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Fractures in children are common; prospective cohort studies suggest narrower bones predispose to fracture. Early life events can influence later growth and development. Observational studies suggest children born to mothers with lower vitamin D levels during pregnancy have narrower bones. We investigated the effects of maternal vitamin D deficiency on offspring's bones' response to mechanical loading in a model system.
C57BL/6 female mice ($n=13$) were maintained on a vitamin D replete ($n=7$) or deficient diet for 6 weeks, mated and maintained on their respective diets until offspring weaning. Following birth drinking water was supplemented with 2 mM Ca^{2+}. Weaned female pups then received a vitamin D replete diet. At both 8 and 16 weeks mice underwent non-invasive tibial axial loading with a peak 11N dynamic load applied to the left tibiae 3x weekly for 2 weeks. Mice were sacrificed at 18 weeks. Trabecular and cortical morphometry of fixed tibiae were quantified using a SkyScan 1172 desktop microCT machine. Results show the difference between loaded and contralateral non-loaded tibias by animal, comparing group means $\pm$ SD.
Tibial loading increased cortical bone volume (BV), bone fraction BV/TV and cortical thickness (Ct.Th) in both groups of mice. Offspring of antenatally vitamin D sufficient as opposed to vitamin D deficient dams showed an increase in BV: $32.3\pm4.7\%$ vs $23.6\pm5.4\%$ ($P=0.01$); BV/TV $9.33\%\pm3.6\%$ vs $4.5\pm2.8\%$ and in Ct.Th: $26.5\pm3.9\%$ vs $20.56\pm4.0\%$ ($P=0.02$) and trends to increased cortical porosity: $64.3\pm12.1\%$ vs $46.5\pm20.0\%$ ($P=0.09$), and tissue volume: $25.4\pm4.1\%$ vs $19.8\pm6.6\%$ ($P=0.1$)
Trabecular bone parameters significantly increased in both groups in response to tibial loading; however there were no significant differences between the two groups.
MicroCT demonstrates non-invasive tibial loading induces an osteogenic response in both cortical and trabecular bone in mice exposed to normal or deficient vitamin D levels in utero. However, mice exposed to vitamin D deficiency in utero showed a reduced response to post-natal mechanical loading, with reduced bone volume and thinner cortices. Such bones would be at increased risk of fracture; we speculate that ensuring vitamin D sufficiency during pregnancy could contribute to fracture risk reduction during childhood and later life.
Disclosure
The authors declared no competing interests.
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OC22

Extra vitamin D from food fortification and bone fractures in adolescents: results from the D-tect study
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Background
Improving the general population's vitamin D status through food fortification is part of an ongoing international debate. Vitamin D status during pregnancy may influence the long-term bone health of the offspring; yet conflicting results have been reported and none of the studies have examined paediatric fracture as outcome.
Method
The influence of extra vitamin D exposure during prenatal life and risk of fracture during adolescence was determined by comparing those who were born before and after the termination of a mandatory vitamin D fortification program, applied in Denmark from 1961 to 1985, the effect of which has never been evaluated. For individuals born in 1983–1988, civil registration numbers were linked to the Danish National Patient Registry for incident and recurrent fractures at ages 12–18 years. Semi-parametric multiplicative models for mean functions were used to assess the association between vitamin D exposure and occurrence of fractures, while accounting for season of birth.
Results
A total of 103.569 exposed and 114.210 unexposed individuals were identified. Among those 11.693 exposed and 11.427 unexposed individuals sustained a fracture. Within each season of birth, the wrist/forearm and ankle fracture rates in the exposed individuals were significantly greater than the rate for the unexposed group, e.g. the estimated rate ratio for wrist/forearm fracture comparing exposed to unexposed individuals born November–January: RR = 1.20; 95% CI: 1.12, 1.28. There was no significant association between exposure and the rate of clavicle fractures.

Table 1 Fracture rate per 1000 person-years by gender and exposure status.

	Girls		Boys	
Fracture Type	D+	D-	D+	D-
Clavicle	0.9	0.9	2.5	2.5
Wrist/forearm	10.0	8.8	16.4	15.0
Ankle	2.5	2.1	3.3	2.9
Total	13.4	11.8	22.2	20.4

Conclusion
Among adolescents exposure to extra vitamin D from food fortification during prenatal life, seems related to an increased risk of fractures, in particular wrist/forearm and ankle.
Funding
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Disclosure
The authors declared no competing interests.
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Late Breaking Abstracts

LB1

Maternal vitamin D depletion disrupts neonatal skeletal development in mice

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Fractures in infancy raise the spectre of child abuse; it has been suggested that lack of vitamin D could result in bone abnormalities that could predispose to fractures. We utilised a mouse model system to investigate whether vitamin D deficiency in utero alters early bone growth and development.
C57BL/6 female mice received vitamin D deficient or replete diet for 6 weeks, then mated and continued on their respective diets until weaning. Pups were culled at Day 0 (D0) or Day 22 (D22). A Skyscan 1172 desktop micro CT machine quantified total bone volume per tissue volume (BV/TV) at D0 and cortical morphometry at D22. D0 pups were skeletally stained using alcian blue/alizarin red whole mount stain. Haematoxylin and Eosin (H+E) staining and Osteomeasure histomorphometry analysis were used to visualise and quantify growth plate zone depths.
At D0 no significant differences were observed between antenatal deplete and replete weights 1.35 g±0.10 vs 1.35 g±0.10. At D22 deficient pups weighed significantly less than replete 6.35 g±0.87 vs 9.01 g±0.29 ($P=0.0001$).
Skeletal staining showed vitamin D replete D0 pups to have a greater area of ossified bone tissue within the axial and appendicular skeleton compared to deplete pups.

Table 1

	Vitamin D deficient		Vitamin D replete		
	Mean	S.D.	Mean	S.D.	*P*-value for difference
D0 BV/TV %	1.93	0.22	3.22	1.07	0.03
D22 cortical volume %	0.11	0.04	0.19	0.03	0.004
D22 cortical thickness %	0.06	0.01	0.08	0.01	0.01
D22 cortical porosity %	8.88	1.99	4.8	0.01	0.002
D22 growth plate depth μm	79	0.013	61	0.003	0.007
D22 hypertrophic zone μm	37	0.008	17	0.001	<0.001
D22 ossification zone μm	9	0.000	15	<0.001	<0.001

No significant differences were observed between resting and proliferating zone depths at D22.

Micro CT show pups exposed to vitamin D deficiency in utero to have a reduced BV/TV. Skeletal staining also showed reduced areas of ossified bone tissue within the skeleton. Pup weights and OBN/BP and OCN/BP remained unchanged at D0. At D22 however large significant changes were found in weight, cortical morphometry, epiphyseal growth plate structure and endosteal OBN/BP suggesting vitamin D deficiency in utero to have negative impacts on early stage bone growth and development which are exacerbated with age.

Disclosure
The authors declared no competing interests.

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LB2

Recessive osteogenesis imperfecta caused by missense mutations in SPARC

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Objectives
We sought to identify the disease-causing mutations in two unrelated girls with a clinical diagnosis of osteogenesis imperfecta type IV.
Methods
Whole-exome sequencing and cellular studies in skin fibroblasts were conducted.
Results
We identified two homozygous variants in *SPARC* (NM_003118.3; c.497G>A (p.Arg166His) in individual 1; c.787G>A (p.Glu263Lys) in individual 2). Secreted protein, acidic, cysteine-rich (SPARC) is a glycoprotein that binds to collagen type I and other proteins in the extracellular matrix. Published modeling and site-directed mutagenesis studies had previously shown that the residues substituted by these mutations form an intramolecular salt bridge in SPARC and are essential for the binding of SPARC to collagen type I. The amount of SPARC secreted by skin fibroblasts was reduced in individual 1 but appeared normal in individual 2. The migration of collagen type I alpha chains produced by these fibroblasts was mildly delayed on SDS-PAGE gel, suggesting some over-modification of collagen during triple helical formation. Pulse-chase experiments showed that collagen type I secretion was mildly delayed in skin fibroblasts from both individuals. Analysis of an iliac bone sample from individual 2 showed that trabecular bone was hypermineralized on the material level.
Conclusion
In conclusion, these observations show that homozygous mutations in *SPARC* can give rise to severe bone fragility in humans.
Disclosure
The authors declared no competing interests.

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Oral Posters

OP1

Skeletal and bone material phenotype in recessive osteogenesis imperfecta due to a novel homozygous point mutation in *TMEM38B*

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Osteogenesis imperfecta (OI) classification has recently been broadened to include genes that primarily affect osteoblast differentiation. *TMEM38B* encodes TRIC-B, a ubiquitously expressed monovalent cation-specific channel protein involved in calcium release from the endoplasmic reticulum. How alterations in *TMEM38B* cause OI remains poorly understood and bone matrix characteristics in affected patients have not previously been described.

We present skeletal and bone material characteristics of two children from apparently unrelated Pakistani families. Patient 1 presented with antenatal femoral bowing. Postnatal radiographs at 2 months of age identified excessive periosteal reaction (cloaking) in all long bones, which later consolidated to form rather wide bones and significant coxa vara. Multiple vertebral fractures showed spontaneous but incomplete reshaping over the first 22 months. Patient 2 presented at 11 years of age with multiple vertebral fractures, femoral bowing and low bone mass.

Clonal sequencing of genomic DNA was performed using a custom designed OI gene panel. Iliac bone biopsy was obtained from case 2 to evaluate histomorphometry and bone mineralization density distribution (BMDD) by quantitative backscattered electron imaging.

A novel homozygous point mutation in *TMEM38B* (c.507G > A), predicted to result in a p.Trp169 nonsense change in exon 4 leading to nonsense mediated decay of the protein, was identified in both individuals. Bone histomorphometry revealed thin and isolated trabecular features covered by an extended area of thin osteoid layer, a paucity of osteoblasts and osteoclasts. Concomitantly, mineralizing surface was rather low and mineralizing lag-time prolonged. Bone cortex had normal lamellar pattern, thickness and haversian canals. BMDD was within normal range.

In conclusion, we describe a novel skeletal phenotype associated with bone fragility caused by a *TMEM38B* point mutation. In contrast to OI with collagen-gene mutations characterized by high bone turnover and abnormally high bone matrix mineralization, we observed in our patient rather low bone turnover and apparently normal bone matrix mineralization. The fact that there was no hypermineralization of the mineralized bone matrix is consistent with previous findings in OI cases lacking direct or indirect abnormalities in collagen type I. The exact role of TRIC-B in bone formation and OI pathogenesis remains to be elucidated.

Disclosure

The authors declared no competing interests.

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OP2

Abstract withdrawn.

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OP3

Increase of preosteoclasts and secretion of PDGF-BB by inhibition of cathepsin K activity increases mouse bone mass during development

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Objective

Accretion of bone mass in childhood is dependent on both bone modeling and remodeling. We recently found that preosteoclasts secrete platelet derived growth factor type BB (PDGF-BB) to promote angiogenesis coupling with osteogenesis during both modeling and remodeling. As secretion of PDGF-BB by preosteoclasts can be enhanced through inhibition of cathepsin K activity to increase bone mass in adults, we explored if increase of secretion of PDGF-BB by preosteoclasts could have similar effects on bone mass in young mice.

Methods

Bone parameters of global cathepsin K knockout ($Ctsk^{-/-}$) mice aged 2, 4 and 8 weeks vs wild type littermates were assessed. Additionally, wild type mice were administered either the selective cathepsin k inhibitor, L-235, or vehicle intraperitoneally 5 days per week from age 2 to 6 weeks. Microcomputed tomography and histological analysis with tartrate resistance acid phosphatase staining and immunostaining for osterix and osteocalcin were analyzed.

Results

$Ctsk^{-/-}$ mice were found to have a statistically significant increase in bone trabecular volume and osteoclast and osteoblast numbers at 2, 4, and 8 weeks of age compared to their aged-matched wild type littermates. Wild type mice treated with L-235 from 2–6 weeks of age showed a statistically significantly higher bone volume per tissue volume and trabecular number with decreased trabecular spacing compared to vehicle-treated wild type littermates. No difference was noted in cortical bone parameters. Histologic studies confirmed similar findings as those to ovariectomized-mouse models with an increase in preosteoclast numbers as well as osteoprogenitors and mature osteoblasts compared to vehicle-treated wild type littermates.

Conclusion

These preliminary data suggest that cathepsin K inhibition can increase bone mass by increasing preosteoclasts and secretion of PDGF-BB in young mice. Future studies are underway to study the ability to enhance bone mass in young osteoporotic animal models.

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Disclosure

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OP4

Transplantation of culture-expanded bone marrow cells and platelet rich plasma in lower limb lengthening for short stature patients

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Objectives

We have performed a novel cell therapy using culture-expanded bone marrow cells (BMC) and platelet rich plasma (PRP) during limb lengthening procedure since 2002. In the present study, we evaluated the efficacy of the cell therapy on new bone regenerates in patients with achondroplasia (ACH) and hypochondroplasia (HCH).

Methods

The transplantation technique of BMC and PRP was described previously (Bone 40: 522–528, 2007). Inclusion criteria of this study were ACH or HCH patients who underwent lower limb lengthening at out hospital and followed up at least 12 months after removal of the fixation pins. A total of 37 patients (112 legs) were included and these patients were separated into two groups; the BMC group that was treated with BMC and PRP transplantation, and control group that had no additional cell therapy. Clinical outcome was defined as either good (healing index of 50 days/cm or less with no adverse events that required any additional treatment) or poor (healing index of more than 50 days/cm or needed additional procedures with or without surgical intervention). Age at surgery, the amount of length gained, and clinical outcome was compared between the two groups.

Results

The BMC group consisted of 68 legs in 23 patients while the control group consisted of 44 legs in 14 patients. There were no significant differences in the age of surgery and the length gained between the two groups. Good outcome, on the

other hand, was significantly higher in the BMC group than in the control group (Table 1).

Table 1 Comparison of the parameters between the BMC and control groups.

	BMC group	Control group	*P* value
Age at surgery (years)	14.6±3.8	16.1±4.3	0.1382
Length gained (cm)	9.2±1.2	8.7±1.7	0.2174
Good outcome (%)	83.8	61.4	0.0073*

Conclusion
Transplantation of BMC and PRP provided better clinical outcome in lower limb lengthening for short stature patients.
Disclosure
The authors declared no competing interests.
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OP5

Osteoclast phenotype of giant multinucleated cells in cherubism may determine the disease aggressiveness

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Cherubism is a rare genetic disorder characterized by extensive growth of a bilateral granuloma of the jaws, resulting in facial disfigurement.
Histologically, the lesions consist of a fibrotic stroma with osteoclastic-like multinuclear giant cells (MGC). Cherubism is caused by gain-of-function mutations in the SH3BP2 protein. SH3BP2 is an intracellular adaptor protein positively regulating the activity of the nuclear factor of activated T-cells c1 (NFATc1), a regulator of osteoclastogenesis. Lysosomal enzyme tartrate resistant acid phosphatase (TRAP) activity is also known to increase with the osteoclastogenesis.
The expressiveness of the disease is highly variable, ranging from almost asymptomatic forms to some life threatening. Presently, there are no prognostic factors clearly identified concerning the severity of cherubism in the literature. The aim of this study is to evaluate the NFATc1 staining and TRAP activity in cherubism tumor, and correlate the results to clinical, radiological, and pathological features to define prognostic factors of the disease.
We performed a retrospective study in nine cherubism patients. Severity of cherubism was graded according to their radiological jaw involvement and to their evolution after surgery. Genetic mutations, pathological features, NFTAc1 staining and TRAP activity were evaluated for each patients.
Three cherubism were graded as low aggressiveness (grade A), four moderate aggressiveness (grade B), and two very severe diseases (grade D). SH3BP2 mutations were found in seven patients, six mutations 1244 and one mutation 1353.Pathological examinations were non significantly different between the three grade groups. In grade A and grade B tumors, all GMC were TRAP negative and negative for NFTAc1 nuclear staining. In all grade D tumors, MGC were all TRAP positive, and displayed nuclear NFTAc1 staining. TRAP activity and NFTAc1 staining were significantly different from grade D tumors to B and A.
TRAP Activity and nuclear NFTAc1 staining is associated with severe cherubism. These two tests can be added to routine pathological examination, to evaluate the prognosis of cherubism, and to adapt treatment. These results suggest that MGC displayed osteoclast characteristic in aggressive tumor, and macrophages characteristic in non-aggressive tumors. Nuclear NFTAc1 activity in aggressive tumor suggest that medical therapy, such as anti-calcineurin could be appropriate to cure aggressive cherubism
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Disclosure
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OP6

Genetic variation is involved in impairment of bone mineral density in long-term adult survivors of childhood cancer

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Introduction
Despite similarities in upfront treatment, impairment of bone mineral density(BMD) varies in long-term adult survivors of childhood cancer (CCS). We studied for the first time whether genetic variation is involved in impairment of BMD in adult long-term CCS.
Method
This cross-sectional single-center cohort study included 334 adult CCS (median follow-up time: 15.2 years (range 5.1–39.8); median age at follow-up: 26.1 years (range 18.1–49.3)). Total body BMD (BMD_{TB}) and lumbar spine BMD (BMD_{LS}) were measured by dual-X-ray absorptiometry(DXA), and BMD was expressed as age-matched and gender-matched standard deviation scores (SDS; *z*-score). We selected 12 candidate single nucleotide polymorphisms (SNPs) in 11 genes based on results of previous studies in the healthy population (*COL1A1, TNFSF11, TNFRSF11, TNRFSA11B, VDR, ESR1, WLS, LRP5, MTHFR, MTRR, IL6*). Multivariate analyses included, apart from candidate SNPs, patient and treatment characteristics that were univariatly associated with BMD values.
Results
Multivariate analyses revealed that lower $BMD_{TB/LS}$ was associated with lower weight at follow-up ($P<0.01$), BMD_{TB} was associated with previously administered radiotherapy($P=0.01$). Survivors with the homozygous minor allele (GG) genotype of rs2504063 (in *ESR1*: estrogen receptor type 1) had a lower BMD_{TB} (-1.17 vs -0.84; $P=0.01$) than those with the AG/AA genotype, however BMD_{LS} was not altered. Carriers of two minor alleles (GG) of rs599083 (*LRP5*: low-density lipoprotein receptor) revealed lower BMD_{TB} (-1.18 vs -083; $P=0.04$), and lower BMD_{LS} values (-0.97 vs -0.54; $P=0.02$) than those with the TT/TG genotype. Carriers of *VDR* (vitamin D receptor) haplotype 3 had a lower BMD_{LS} than non-carriers (-0.86 vs -0.64, $P=0.05$), but BMD_{TB} was not altered.
Conclusion
CCS who are carriers of candidate SNPs in the *VDR*, *ESR1* or *LRP5* genes seem to be more vulnerable to impaired bone mass at an early adult age. In addition to patient and treatment related factors, information on genetic variation in cancer patients may be helpful in identifying survivors who are at risk for low bone density after childhood cancer treatment.
Disclosure
The authors declared no competing interests.
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OP7

Lessons from homocystinuria: Cystathionine beta-synthase as a novel marker for osteogenic differentiation of human mesenchymal stem cells

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Objective
Classical homocystinuria due to cystathionine beta-synthase (CBS) deficiency, is a rare autosomal recessively inherited disease characterized by the multiple involvement on different organs. While the most striking cause of morbidity and mortality is thromboembolism, patients develop a marked osteoporosis at early age along with many other skeletal abnormalities. As CBS normally converts homocysteine to cystathionine, the result of CBS deficiency is an accumulation of homocysteine. However, it seems to be conceivable that other mechanisms than high levels of homocysteine cause the defect in bone homeostasis, as betaine, the gold standard therapy for thromboembolism, is unable to completely prevent osteoporosis. Restoration of Hydrogen sulfide (H_2S) levels in CBS knockout mice has been recently found to restore the BMMSC impairment and osteopenic phenotype. However CBS-H_2S regulation of physiologic bone homeostasis is far from being fully elucidated. In particular, whether CBS expression is linked to the process of osteogenic differentiation of human MSCs is still unclear.

Methods
In vitro osteogenic differentiation of h-MSCs; *ex-vivo* comparison of h-MSCs and mature h-OBs and *in vivo* expression in human bone tissue biopsies were performed. h-MSC were separated into 'mineralizing' vs 'non-mineraling' based on Alizarin Red staining quantification at the end of culture. CBS and alkaline phosphatase (ALP) expression were evaluated by RT-PCR, immunohistochemistry and Western blot analyses.
Results
CBS was found to be expressed in human bone tissue as well as in *ex-vivo* primary cultures of bone cells. CBS expression was selectively up-regulated in h-MSCs undergoing mineralization ($P<0.0001$) while ALP was up-regulated in both mineralizing and non mineralizing h-MSCs ($P<0.01$). As a consequence, CBS expression significantly correlated ($P<0.0001$) with *in vitro* mineralization and outperformed ALP as a marker of mineralization. Consistently, CBS expression was significantly higher in mature h-OBs vs h-MSCs obtained from same patients ($P<0.001$). Finally, stimulation of h-MSCs with exogenous H_2S (50–200 μM) significantly stimulated ($P<0.05$), while pharmacological inhibition of CBS partially abrogated, *in vitro* mineralization.
Conclusions
CBS expression is unexpectedly correlated to the osteogenic differentiation of h-MSCs and identifies a new marker of mineralization behaviour. Moreover, functional data support the hypothesis that H_2S may be the link between defective CBS and low bone mass in homocystinuria.
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Disclosure
The authors declared no competing interests.
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OP8

Characterising the muscle-bone unit in children and adolescents with and without cystic fibrosis using novel imaging techniques and jumping mechanography

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Cystic fibrosis(CF) results in low volumetric bone mineral density(vBMD), poor muscle strength and increased fracture risk in young patients. The aim of this study was to compare bone and muscle variables measured by peripheral and high-resolution QCT (pQCT and HR-pQCT) and jumping mechanography (JM) In CF children and healthy controls. We hypothesised that CF children have lower muscle force and power (Fmax and Pmax) than controls which may contribute to CF-related bone disease.
216 children (65 CF) aged 8–16 years had pQCT scans and JM measurements; 176 (25 CF) had HR-pQCT scans. Fmax and Pmax were measured using JM. Volumetric BMD, CSA, stress strain index (SSI) and microarchitecture were measured at the 4% (pQCT), 66% (pQCT) and 8% (HR-pQCT) sites of the tibia. Group differences, with appropriate interactions, were tested using multiple regression adjusting for maturity and body size and, in a separate model, additionally for Fmax and Pmax. Data are presented as β-coefficient (%) and *P*-value.
CF children had lower vBMD (6–8%, $P<0.001$), smaller bones (10%, $P<0.001$) with less cortical CSA (4%, $P<0.01$) and thinner trabeculae (12%, $P<0.05$). After adjustment for Fmax and Pmax, cortical vBMD (4%, $P<0.001$) and BV/TV (29%, $P<0.01$) were lower in CF children. CF children had lower cortical vBMD ($P<0.001$) and Tb.Th ($P<0.05$) compared to controls at the same stage of puberty, a difference that was greater at late puberty. The CF group had lower total vBMD ($P<0.05$), BV/TV ($P<0.001$), and Tb.N ($P<0.01$) compared to controls for a given Fmax and this difference was greater at higher Fmax. There was a negative relationship between Pmax and BV/TV ($P<0.01$) and Tb.N ($P<0.05$) in CF children and in controls. BV/TV and Tb.N did not differ with greater Pmax in controls.
Group differences in bone measures existed after adjusting for sex, maturity, and body size. The attenuation of group differences, except BV/TV, after adjustment for Fmax and Pmax indicates a role for muscle in bone development. The interactions suggest a less efficient adaptation to muscle forces in bones of CF and possible worsening bone disease with puberty, both of which may contribute to the increased fracture risk in CF adolescents and adults.
Disclosure
The authors declared no competing interests.
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OP9

Growth, body mass index, bone health and ambulatory status of boys with Duchenne Muscular Dystrophy treated with daily vs intermittent oral glucocorticoid regimen

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Background
Oral glucocorticoids (GC; prednisolone dose of 0.75 mg/kg per day), help to preserve muscle strength and prolong independent walking in boys with DMD. This study compared longitudinal growth, body mass index (BMI), bone mineral density (BMD), vertebral fractures (VFs) and ambulatory status in boys with DMD on daily (DAILY) or intermittent (INTER; 10 days on & 10 days off), oral GC regimens.
Methods
50 DMD boys from two UK centres were included in the study; 25 boys each were on the DAILY or the INTER regimen. Size adjusted lumbar spine BMD (LS BMAD), total body less head BMD (TBLH), VF assessment and forearm pQCT data were analysed in all boys at three time points; baseline, 1 and 2 years.
Results
At their first (baseline) assessment, there were no significant differences in mean (S.D.) age (8.3 (2.5) years) or any of the bone parameters, but DAILY boys were already shorter ($P=0.013$) with higher BMI ($P=0.014$). There were no documented VFs; however 1 DAILY and three INTER boys had suffered long bone fractures. All DAILY boys were still ambulant whereas five INTER boys had already stopped walking. Prior to the 2 year assessment, six of the DAILY boys had sustained symptomatic VFs and were subsequently commenced on IV bisphosphonate therapy; these boys were excluded from further follow-up bone parameter comparisons. At 2 years, six DAILY boys and ten INTER boys had lost ambulation and the difference in height between DAILY and INTER boys had increased significantly ($P<0.001$). The DAILY boys also had significantly higher BMI SDS but lower BMAD and TBLH *z*-scores. Most notably, significantly more DAILY boys had VFs compared to INTER boys (13 DAILY vs four INTER; $P=0.015$). Only two of the 16 boys with VFs also had low BMAD ($z<-2$); in contrast 14 had low TBLH BMD *z*-scores and 11 had low trabecular BMD *z*-scores.
Conclusion
Boys on a daily GC regimen appear to remain ambulant longer but at the cost of significantly greater VFs, greater adiposity and markedly diminished growth. In contrast, the boys on the intermittent GC regimen had fewer fractures but lost ambulation earlier. In both groups, LS BMAD was a poor predictor of VFs.
Disclosure
The authors declared no competing interests.
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OP10

Does degree of adiposity influence upper limb fracture site in children?

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Although it has been suggested that overweight and obese children have an increased risk of fracture, recent studies in post-menopausal women have shown that the relationship between obesity and fracture risk varies by fracture site. Thus, obesity is protective against wrist fractures but confers an increased risk of humeral fractures. There are no data to suggest whether this observation is also present in children. We therefore assessed whether adiposity and overweight/-obesity prevalence differed by upper limb fracture site in children.
Height, weight, BMI, triceps and subscapular skinfold thickness (SFT) were measured in children aged 3–18 years with an acute upper limb fracture. Overweight and obesity were defined as a BMI z-score $\geqslant 1.036$ (85th centile) and $\geqslant 1.645$ (95th centile) respectively to allow comparison to the 2012 United Kingdom Health Survey for England prevalence of childhood overweight and obesity (27.9%). Data was compared across three fracture sites (hand, forearm and upper arm/shoulder (UA)).

401 children (67.1% male, median age 11.7 years (range 3.5–17.3 years)) participated. 34.2%, 50.6% and 15.2% had fractures of the hand, forearm and UA respectively. After adjustment for age and sex, children with forearm fractures had higher weight, BMI and SFT z-scores than those with UA fractures ($P<0.05$ for all). There were no differences between children with hand and forearm or hand and UA fractures.

Overweight and obesity were more prevalent in children with forearm fractures (37.6%) than those with UA fractures (19.0%, $P=0.009$). In comparison to United Kingdom population, the prevalence of overweight and obesity was higher in children with forearm fractures (p=0.003), whereas children with either UA ($P=0.13$) or hand fractures (29.1%, $P=0.76$) did not differ.

Measurements of adiposity and the prevalence of overweight/obesity differed by fracture site in children with upper limb fractures. Children with forearm fractures had the highest indices of adiposity.

Disclosure

The authors declared no competing interests.

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OP11

Optimal dose of calcium for treatment of nutritional rickets

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Objective

Nutritional rickets in Nigerian children is primarily due to dietary calcium deficiency and heals with calcium supplementation. Our aim was to determine the optimal dose of calcium for treatment of children with rickets due to dietary calcium deficiency.

Methods

At the Jos University Teaching Hospital, 65 Nigerian children with radiographically-confirmed rickets were randomized to daily supplemental calcium intake of 500 mg ($n=21$), 1000 mg ($n=23$), or 2000 mg ($n=21$). Venous blood, radiographs, and forearm bone density (BMD) were obtained at baseline and at 8, 16, and 24 weeks after enrollment. The primary outcome was radiographic healing, assessed with a 10-point radiographic score (score of 10 represents the most severe rickets, and 1.5 or less is considered healed).

Results

The radiographic severity scores improved in all three groups over 24 weeks, but the rate of radiographic healing differed significantly between groups. The 1000 and 2000 mg supplementation groups improved significantly more rapidly ($P<0.001$) than the 500 mg supplementation group during treatment (Figure 1). The 2000 mg group did not heal more rapidly than the 1000 mg group. After 24 weeks, 12 (67%), 20 (87%), and 14 (67%) in the 2000, 1000, and 500 mg groups respectively, had achieved a radiographic score of 1.5 or less ($P=0.21$). Alkaline phosphatase decreased and serum calcium increased at similar rates in all groups. The forearm diaphyseal BMD improved significantly more rapidly in the 2000 and 1000 mg groups than in the 500 mg group ($P<0.001$).

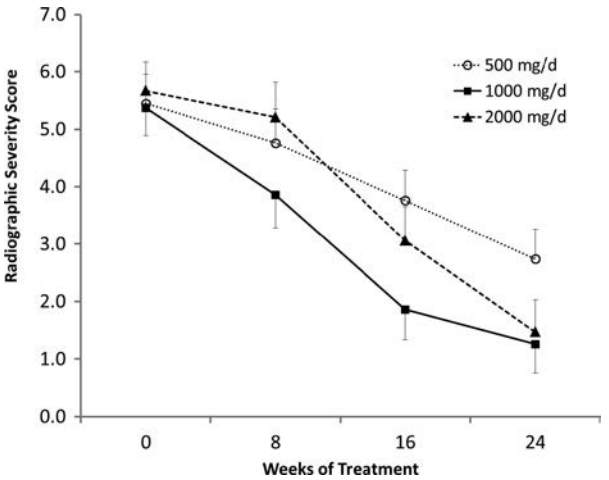

Figure 1 Radiographic scores during treatment of nutritional rickets with three different doses of calcium supplements

Conclusion

Daily calcium intakes of 1000 or 2000 mg were superior to 500 mg for radiographic healing of rickets, but 2000 mg did not improve radiographic scores more rapidly than 1000 mg.

Disclosure

The authors declared no competing interests.

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OP12

A non-invasive method for screening vitamin D insufficiency for adolescents using skin colourimetry

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Introduction

Effective screening for vitamin D (Vit-D) insufficiency is desirable. Pigmentation of unexposed (constitutive) skin and exposed (facultative) skin can be measured with skin colourimetry to assess dermal capability in synthesizing Vit-D and degree of sunlight exposure respectively. This study aimed at evaluating whether skin colourimetry could be used to screen Vit-D insufficiency among adolescents.

Methods

240 healthy adolescents (mean age=14.5 years) were recruited. Serum 25 (OH) Vit-D was assayed, skin pigmentation (in ITA, or individual typology angle) was measured with Konica-Minolta CM-2300d Skin Colourimeter and dietary Vit-D intake was evaluated. Multivariate linear and logistic regression models were used for analysis.

Results

The most significant constitutive and facultative skin locations were the non-dominant instep ($P=0.021$) and the non-dominant dorsum of hand ($P=0.008$) respectively. Logistic regression analysis showed ITA (instep) and ITA (dorsum) were significant factors for predicting Vit-D insufficiency ($P=0.001$) yielding the following predictive equation:

Log (Pred/(1-Pred))=0.072(ITA(dorsum)) – 0.095(ITA(instep)) – 0.09(season) – 0.297(gender) – 0.005(BMI) – 0.29 (age)+8.055.

The ROC curve (Figure 1) gave an area under curve (AUC) of 0.70 (95% CI: 0.63–0.78) with sensitivity of 0.80 and specificity of 0.48 at a predicted probability cut-off of 0.61.

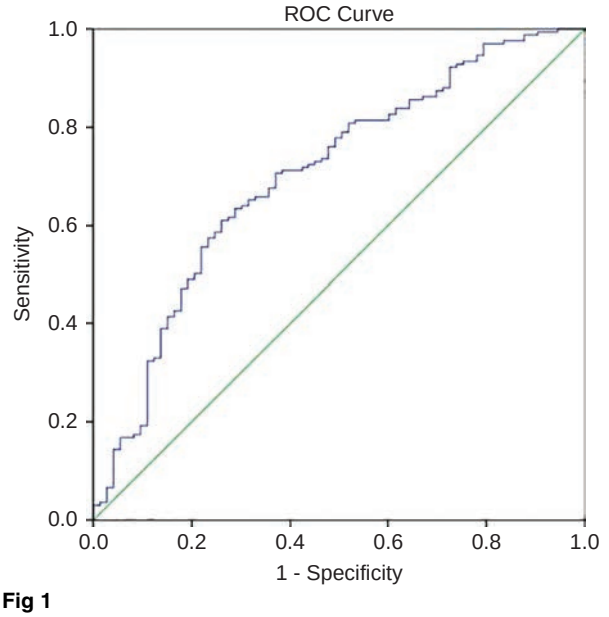

Fig 1

Subgroup analysis for females with dietary Vit-D intake < 400 IU per day gave an even better ROC curve with AUC of 0.80 (95% CI: 0.69–0.91), sensitivity of 0.81 and specificity of 0.71 at a predicted probability cut-off of 0.74.

Conclusion

This study gave strong evidences that skin colourimetry could be applied for screening Vit-D insufficiency. ITA could be measured swiftly and the results indicating the likelihood of Vit-D insufficiency could be obtained. This study carries significant clinical impacts in that individual awareness and early detection of the condition at its asymptomatic stage can be achieved thus helping to tackle the epidemic of Vit-D insufficiency in the general population.

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Disclosure

The authors declared no competing interests.

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Poster Presentations

P1

Abstract withdrawn

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P2

The assessment of bone regulatory pathways in children with malignant bone tumors

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Objectives
As the receptor activator of the nuclear factor κB (RANK)/receptor activator of the nuclear factor κB ligand (RANKL)/osteoprotegerin (OPG) cytokine system is essential for osteoclastogenesis and Wnt signaling pathway for osteoblastogenesis, we decided to assess these two main bone regulatory pathways in patients with malignant bone tumors on the completion of anticancer therapy.
Methods
The study included 35 patients (median age 15.0 years) with diagnosed malignant bone tumors (25 patients with osteosarcoma, ten patients with Ewing sarcoma) treated at the Department of Surgical Oncology for Children and Youth at the Institute of Mother and Child in Warsaw. All patients were treated with preoperative chemotherapy, after which surgery was performed and then they were administrated postoperative chemotherapy. After completion of treatment (about 2 months after last course of postoperative chemotherapy) densitometry scans were performed and biochemical bone metabolism parameters were determined. Total bone mineral density (BMD) and lumbar spine BMD measurement was performed by dual energy-ray absorptiometry (DXA). Bone metabolism markers (RANKL, OPG, sclerostin, Dickkopf-related protein 1 – Dkk-1) were determined by immunoenzymatic assays. The obtained results were compared with the control group consisting of 30 healthy children (median age 14.5 years) without diseases that may influence bone metabolism. This study was approved by the Ethics Committee of the Institute of Mother and Child.
Results
In patients with bone tumors, we determined comparable to controls concentration of sclerostin (0.40 vs 0.43 ng/ml) and lower by about 15% concentration of Dkk-1 (1.66 vs 1.95 ng/ml). Additionally, we observed higher median value ($P<0.05$) of RANKL in the patient group and similar concentration of osteoprotegerin in both studied groups. The ratios of RANKL/OPG and sclerostin/Dkk-1 were slightly higher in patients than in the controls (0.34 vs 0.30 and 0.24 vs 0.22 respectively). We observed also reduced z-score total BMD (-1.15 vs 0.21; $P<0.01$) and z-score BMDL1-L4 (-1.03 vs -0.02; $P<0.01$) in patients after anticancer treatment compared with the control group.
Conclusion
We found alterations in both bone regulatory pathways in patients with bone tumors after anticancer treatment. These changes may be related to lower bone mineral density in these patients.
Disclosure
The authors declared no competing interests.

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P3

PHEX, DMP1 and FGF23 mutations in a Malaysian hypophosphatemic rickets patient

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Hypophosphatemic rickets (HR) is a type of bone disorder that causes skeletal deformities due to reduced renal phosphate reabsorption that affect bone mineralisation. Defect on *PHEX*, *DMP1* and *FGF23* causes x-linked dominant, autosomal recessive and autosomal dominant HR respectively. The aim of this study was to identify the underlying genetic mutations in *PHEX*, *DMP1* and *FGF23* in a 15-year-old female who exhibits the clinical features of HR that was confirmed by laboratory tests and radiological assessment. The parents and her two other siblings did not show any clinical symptoms of HR. Genetic variations in these genes were assessed using polymerase chain reaction and direct sequencing of coding exons and flanking intronic regions. The proband was found to have mismatch mutations in all three genes leading to amino acid changes at c.10G>C, (p.E4Q), c.205A>T (p.S69C), and c.716C>T (p.T239M) in *PHEX*, *DMP1* and *FGF23* respectively (Figure 1). Based on SIFT and PolyPhen, *tools* that predict functional impact of amino acid changes, E4Q mutation in *PHEX* was evaluated as tolerable and probably damaging respectively. The tools predicted the mutation found in *DMP1* (S69C) as damaging and probably damaging, while T239M mutation in *FGF23* as tolerable and benign respectively. E4Q and S69C mutations had been reported to affect bone mineralisation and causes hypophosphatemia in HR patients[1,2], while T239M mutation has been linked to renal phosphate leak in hypophosphatemic nephrolithiasis[3]. The presence of three mutations in genes related to HR probably was the reason for severe clinical manifestations of HR in this patient. The molecular diagnosis confirmed the clinical diagnosis of HR in this patient and contributes significantly to genetic counselling and helps improve patient clinical care and management.

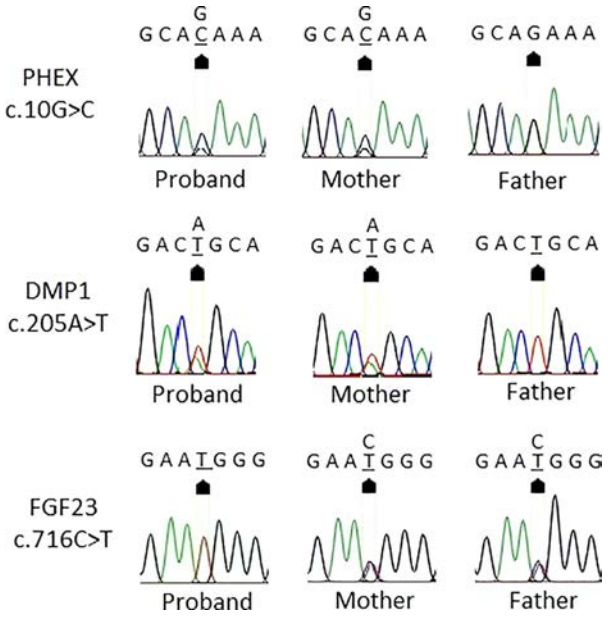

Figure 1 Mutation analysis of *PHEX*, *DMP1* and *FGF23* of a Malaysian family with hypophosphatemic rickets daughter. The proband was heterozygous for *PHEX* (c.10G>C, p.E4Q) and *DMP1* (c.205A>T, p.S69C), and homozygous for *FGF23* (c.716C>T, p.T239M) missense mutations. Her unaffected mother had both the mutant and wild-type alleles for all the mutations. The asymptomatic father carried homozygous wild-type allele, homozygous mutant allele and heterozygous alleles for *PHEX*, *DMP1* and *FGF23* respectively.

Disclosure
The authors declared no competing interests.
References
1. St-Louis M. *Contrôle de l'expression de la protéine PHEX et rôle de PHEX et FGF23 dans la minéralisation par les cellules MC3T3*. Doctoral dissertation. Université de Montréal, Quebec, Canada. 2009.
2. Turan S, Bastepe M, Bereket A, *et al.* Identification of Novel Dentin Matrix Protein-1 (DMP1) Mutations in Two Unrelated Kindreds with Autosomal Recessive Hypophosphatemia. *SABMR 29th Annual Meeting. Journal of Bone and Mineral Research*, 2007 **22**: 402–451. doi: 10.1002/jbmr.5650221410.
3. Rendina D, Esposito T, Mossetti G, *et al.* A functional allelic variant of the FGF23 gene is associated with renal phosphate leak in calcium nephrolithiasis. *The Journal of clinical endocrinology and metabolism*, 2012 **97**(5): E840–4. doi:10.1210/jc.2011-1528.

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P4

Bone turnover markers and bone mineral density after 12-month weight loss therapy in obese children

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Objectives
Weight loss therapy is the principal non-pharmacological method for prevention and treatment of simple obesity in childhood. This intervention may influence bone metabolism in children, but this phenomenon is not well understood. The aim of this study was to assess the changes in body composition and in the profile of bone markers after weight loss in obese prepubertal children.
Methods
We determined serum BALP (bone alkaline phosphatase), CTX-I (C-terminal telopeptide of type I collagen) and OC (osteocalcin) by ELISA kits. Biochemical markers, body composition and bone mineral density (assessed by dual-energy x-ray absorptiometry) were studied in 30 obese children (z-score BMI >2) before and after 12 months of lifestyle intervention (low-energy diet, physical activity). The recommended daily energy intake was 1200–1400 kcal per day. The diet was composed of 20% protein, 30% fat and 50% carbohydrates. The control group consisted of 30 non-obese children (z-score BMI $<-1+1>$). This study was approved by the Ethics Committee of the Institute of Mother and Child.
Results
Obese children had higher BALP activity by about 20% ($P<0.001$) and similar values of CTX-I and OC compared with non-obese children. In patients after therapy, we observed decrease of BMI value by about 10% ($P<0.001$) and lower percent of body fat mass ($41.0\pm5.0\%$ vs $36.1\pm4.7\%$; $P<0.001$). After weight loss the BALP and OC values in obese patients were unchanged, whereas CTX-I concentration increased by about 10% ($P<0.05$). z-score total BMD and Z-score BMD L2–L4 in obese children before therapy were higher than in controls ($P<0.001$) and significantly decreased after therapy ($p<0.01$).
Conclusion
Our results suggest that obesity during the prepubertal period is associated with alterations in the profile of bone markers and greater whole-body bone mass as a result of increased bone formation rather than reduced bone resorption. The changes in bone metabolism after 12-month lifestyle intervention seem to be related to alterations in bone resorption process.
Disclosure
The authors declared no competing interests.

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P5

Vitamin D and decreased bone density in children

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Aim
Determining level of vitamin D and other conditions in children with osteoporosis.
Methodology
Bibliography review in a worldwide basis about the issue and what we have observed.
Outcome
We studied the level of 25OHD3 in all patients with osteoporosis and osteopenia. 25OHD3 95% deficit was found in these patients when reduced bone mass occurs. There are several disorders for hypocalcemia. Intestinal malabsorption syndromes, recognizable by low concentrations of 25 hydroxyvitamin D3. Usually there is assotiation of fat malabsorption with liver failure in the aetiology of vitamin D deficiency. Paying attention to bone loss and fracture as to osteoporosis after liver transplantation. Other conditions which causes reduced bone mass are hypercalciuria, hypocalcemia, idiopatic juvenile osteoporosis, osteogenesis imperfecta, nutritional rickets, hypophosphatemic rickets, bone mineral metabolism disorders, osseous heteroplasia, fibrous dysplasia, pseudo-hypoparathyroidism, goitre, hypothyroidism, hyperthyroidism, hypoparathyroid-ism, corticosteroids, goitre and thyroidism treatment, muscular diseases, calcium, phosphorus fat and protein disorders, hypergonadotrophic and hypogonadotrophic hypogonadism, Turner's and Down syndrome, renal diseases, cystic fibrosis, eating disorders and no physical activity. Chronic liver disease is associated with osteoporosis in children. Bone density is also decreased in the months immediately after liver transplantation. In the case of children, bone accretion is necessary for growth. Chronic liver disease and transplantation in childhood will have an adverse effect on bone metabolism and the outcome after the growth period cannot be predicted.
Discussion and conclusions
Non-pharmacologic approaches are important in osteoporosis-prevention. Include dietary modifications, exercise, determining and treating risk factors and fall prevention. Both calcium and vitamin D supplementation have been associated with reduced bone loss and decreased risk for fractures. Improvement and maintaining of bone health must be started early in life. Weight-bearing progressive physical activity. Treatment consist in acting on aetiology of decalcification, decreasing it and increasing calcium in bones, mild antiresorptive, strontium ranelate and teriparatide according as age. If female hypogonadism hormone replacement therapy, best *via* the transdermal route in patients with malabsorption or liver disease, is advised for the prevention of osteoporosis. As in other organ transplant recipients, bone loss occurs rapidly, so therapy is optimally started before or at the time pre-orthotopic liver transplantation.
Disclosure
The authors declared no competing interests.

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P6

Bisphosphonate treatment of melorheostosis: A case report

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Background
Melorheostosis also known as Leri's disease or flowing periostal hyperostosis is a rare nonfamilial sclerosing bony dysplasia of poorly understood etiology. It is characterised by soft Tissue contractures with overlying slowly evolving linear hyperostosis. Radiographic findings are helpful in the diagnosis, these consist of irregular hyperostosis extending along the length of one side of the long bone, resembling flowing candle wax. Treatment is mainly symptomatic including bisphosphonates. We reported a case melorheostosis involving the foots, hands and the tibia which was improved by pamidronate treatment.
Presenting problem
A 15 years-old female had chronic pain around her foots and hands, and had been unable to wear shoes because of toe deformity for last 6 months. She stated that her foot hurt in shoe gear. She often tripped when she was running and playing. The physical exam revealed a severely 'C' shaped right foot that was nonreducible, and an irregular bony surface was palpated, and erythematous change and callosity formation were seen around the contact area between the skin and the shoes. Biochemical findings were within the normal range (Ca, P, ALP, PTH, 1-25(OH)2 Vit-D, calcitonin), but FGF-23 level was high compared with normal ranges for age. Genetic analysis did not show LEMD3 gene defect. Radiological examination showed that distal part of the radius and metacarpal and carpal phalanges 2–3 and metatarsal phalanges were thickened and sclerosed. The interphalangeal soft tissues show diffuse swelling.
Clinical management
She was treated with sodium pamidronate (1 mg/kg per day, 3 days each mounts) for 9 mounts. End of this period swelling in the hands and foots decreased and the pain abated.
Discussion
Treatment is mainly symptomatic including bisphosphonates in patients with melorheostosis. Non steroid antiinflamatuvar drugs, nifedipine and even sympathetic blockers have been prescribed in a attempt to alleviate pain with variable results. Bisphosphantes when used at high concentration have antiinflammatory effects by inhibiting production of proinflammatory cytokines, and may help to decrease pain.
Disclosure
The authors declared no competing interests.

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P7

History of meconium ileus affects bone health and body composition in young patients with cystic fibrosis

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Objective
Growth of patients with cystic fibrosis (CF) and meconium ileus is frequently compromised. The aim of this prospective study was to evaluate body composition in this particular group of patients. We hypothesized that history of meconium ileus could predict suboptimal growth, bone, muscle and fat mass, irrespective of other prognostic factors for CF.
Methods
CF subjects were investigated over a 3-year period. Their medical records were reviewed and the following data were collected: forced expiratory volume in 1 sec (% predicted value, FEV1%), 25(OH) D levels, CF mutation, presence of diabetes mellitus and pancreatic insufficiency, systemic steroid courses/year, fracture history, dietary calcium intake and exercise. All patients were examined and their weight, height and BMI were recorded and expressed as z-scores. Then, dual-energy x-ray absorptiometry (DXA) was performed, at the lumbar spine and total body (less head, TBLH). Bone mineral density (BMD), lean tissue mass (LTM) and fat mass (FM) were measured and z-scores were calculated. Finally, CF patients with a history of meconium ileus were compared to participants with no such history.
Results
A total of 101 patients with CF and pancreatic insufficiency were assessed (mean age 13.9 ± 2.9 years, 79 females, 81 adolescents). Of all patients, 19 had a history of meconium ileus; they were significantly different from the other patients in terms of BMI, BMD TBLH, LTM and FM z-scores, as well as FEV1%.
History of meconium ileus was associated with low fat mass (OR = 5.38, $P = 0.002$); the relation with BMD TBLH z-score and LTM z-score was not statistically significant, with a marginal P-value of 0.051 and 0.056 respectively. The significant association between a history of meconium ileus and low fat mass persisted after adjustments for age, CF genotype, degree of lower airway obstruction and need for systemic steroids.
Conclusion
History of meconium ileus in CF patients could be a predisposing factor to low BMI and fat mass, whereas cortical bone and muscle mass are only marginally affected. Patients with this profile should be targeted towards prompt nutritional interventions and regular surveillance of their body composition profile.
Disclosure
The authors declared no competing interests.

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P8

Body composition profile of patients with Duchenne muscular dystrophy living in a country with the obesity epidemic

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Objectives
To evaluate bone health and body composition in Greek patients with Duchenne muscular dystrophy (DMD), hypothesizing that prepubertal patients would not be fatter than controls, given the Greek obesity epidemic. Greece ranks among the first countries in overweight and obesity prevalence globally; 30 and 13% of childhood population respectively.
Methods
Cross-sectional study, conducted at the Greek Institute of Child Health (Athens) over a 2-year period. Steroid-dependent DMD subjects underwent dual-energy x-ray absorptiometry (DXA) and laboratory evaluation and were compared to a group of healthy Greek boys.
Results
42 patients and thirty-one controls were studied. 26 patients were on prednisolone and sixteen were on deflazacort. 11 DMD subjects were using a wheelchair and all of them had reached puberty. Seven patients sustained a total of eight fractures, of which four were verterbral. Overall, DMD subjects were shorter (height z-score = -1.4, $P = 0.01$). Their bone mineral density (BMD) was low (lumbar spine BMD z-score = -1.2, $P < 0.01$, subcranial total body BMD z-score = -1.8, $P < 0.01$). Lean tissue mass (LTM) was also decreased (LTM z-score = -2.2, $P < 0.01$). The above findings were more pronounced in adolescence, when loss of ambulation occurs. Regarding adiposity, increased fat mass (FM) was found only in pubertal DMD patients (FM z-score = 1.4, $P < 0.01$), whereas prepubertal, able-bodied patients did not differ from controls, thus confirming the initial hypothesis. Finally, 65% of DMD subjects had increased bone resorption markers and 57% had low vitamin D levels, despite supplementation with 400 IU/d of cholecalciferol.
Conclusion
Abnormal body composition and suboptimal bone profile is evident in DMD patients and is more striking during puberty. Regular laboratory and DXA monitoring, starting in the prepubertal period, could aid in prevention of severe osteoporosis, sarcopenia and obesity. Ideally, native reference population should be used in body composition analysis, as it includes subjects living in the same area, with comparable dietary habits and lifestyle.
Disclosure
The authors declared no competing interests.

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P9

Vitamin D supplementation can improve velocity of growth in children with vitamin D deficiency which are in treatment with RHGH for growth hormone deficiency

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Objectives
The correlation between vitamin D and GH–IGF1 axis is documented. Growing children, need extra Vit-D because it is required for growth. Severe deficiency in Vit-D generates poor growth. Height is usually more affected. Growth hormone (GH) deficiency in children causes severe growth retardation, Vit-D deficiency, and osteopenia. The aim of this presentation was: 1. To evaluate the Vit-D blood level to children in substitution treatment with rhGH. 2. To see if there is a correlation between the very low level of Vit.D (< 10 ng/ml) and low answer (low velocity) to therapy with rhGH.
Methods
The study included 105 children and adolescents (56 girls and 49 boys), aged between 0 and 18 years, enrolled in our clinic in treatment with rhGH. To determine vitamin D status we measured serum 25-OH D3 by taking a single blood sample in the morning, in a fasting stage. We categorized vitamin D levels in three subgroups: deficiency (< 10 ng/ml); insufficiency (10–20 ng/ml) and sufficiency (> 20 ng/ml).
Results
The mean level of Vit-D was 18.7 ng/ml. 52% of subjects had the level of Vit-D less than 20 ng/ml, of which 10% with deficiency state. Of the total children followed, 59 were with growth hormone deficiency (GHD) (56%). Of these 54% were girls and 46% boys. At them 55.2% have had a Vit-D level > 20 ng/ml and only 8.8% value < 10 ng/ml. At the last of them we followed velocity on 12 months under treatment with rhGH and then another 12 months under rhGH treatment and with Vit-D supplementation: 500 IU $\times$ 2 of vitamin D3 daily. The velocity increased in second year when GH therapy was associated with the supplement of vitamin D from a mean of 5.5 cm per year to a mean of 8.5 cm per year.
Conclusions
Insufficiency of Vit-D has been found in over 50% of children and adolescents followed by us. Slower growth in children already under replacement treatment with rhGH, could be caused by the low level of Vit-D. Supplementing with Vit-D can improve speed of growth in these children.
Disclosure
The authors declared no competing interests.

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P10

Infantile Blount's disease: histopathologic changes in the proximal tibial metaphysis – comparison between medial and lateral specimens

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Only minor literature on histopathologic changes in Blount's disease is available. This study presents the histologic findings of biopsies harvested from the medial and lateral part of the proximal tibia during the W/M serrated osteotomy in patients with infantile Blount's disease, performed in Ghana. In this study it is hypothesized that the medial metaphyseal area in these children will present a different histological morphology compared to the lateral metaphyseal area.
During two unilateral and two bilateral W/M serrated osteotomies, biopsies of the medial and lateral cortex of the proximal part of the serrations were taken. Patients were included prospectively. The specimens were fixed in formalin, decalcified, embedded in paraffin, sectioned and stained with hematoxylin and eosin, and Safranine O. All specimens were evaluated by light microscopy.
From the medial obtained specimens, 50% showed presence of endochondreal ossification and 33% showed subperiosteal islands of hypertrophied chondrocytes (Figure 1 A–B). In the lateral aspect of the metaphyseal bone no abnormalities were observed.
In conclusion, in patients with infantile Blount's disease disturbed endochondral ossification in the medial part of the proximal tibial metaphysis is observed.

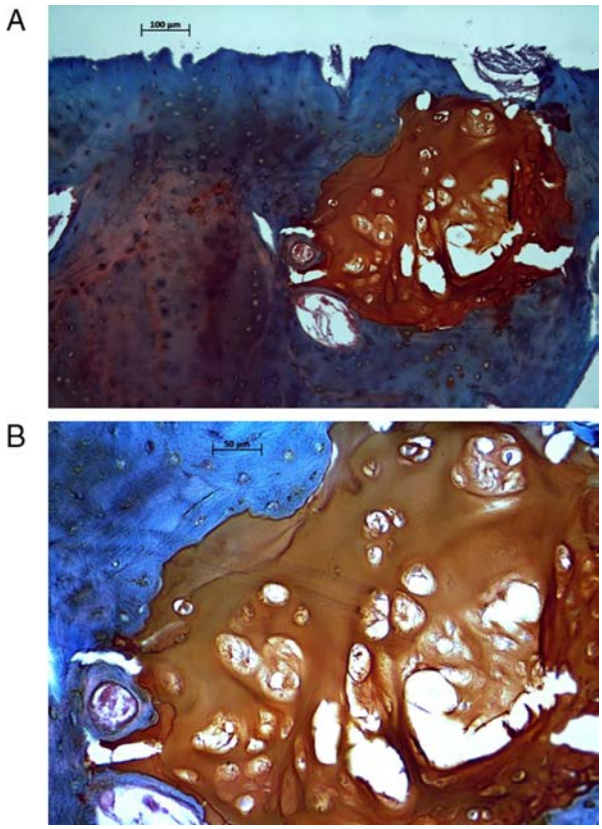

Figure 1 A-B Islands of hypertrophied chondrocytes. A-B. Sections from the medial site of the tibia were stained by Safranin-O/Fast Green to determine the presence of cartilaginous tissue. Bar = 100 µm for first micrograph (A) and bar = 50 µm for second micrograph (B). These figures show islands of densely packed chondrocytes which colour orange like after the Safranine-O/Fast Green staining due to the presence of glycosaminoglycans in cartilaginous tissue.

Disclosure
The authors declared no competing interests.

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P11

Effects of bisphosphonate for the development of scoliosis in children with osteogenesis imperfecta

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Backgrounds
Osteogenesis imperfecta (OI) is an inherited bone disease caused by qualitative or quantitative defects in type I collagen, and is characterized by bone fragility and ligamentous laxity. Spine disorder is an important symptom in children with OI, and respiratory difficulties secondary to spinal disorder were identified as a main cause of death in these patients. Reduced fracture rates and prevention of long-bone deformities have been reported in children with OI who are given bisphosphonates (BPs). However, It is still unknown whether BP therapy prevents the occurrence and progression of scoliosis in children with OI.
Objectives
To clarify the prevalence of scoliosis and determine risk factors for scoliosis development in children with OI who underwent treatment with intravenous pamidronate (PAM).
Methods
Children with OI who had no scoliosis at the first PAM administration and who underwent PAM therapy alone were retrospectively reviewed. Using dual-energy x-ray absorptiometry, we measured the L1–L4 scoliotic angle (Cobb angle) and assessed coronal vertebral deformity over time. We examined the relationship between scoliosis and type of OI (Sillence classification: types I, III, and IV), z-scores of BMD in L2–L4 of the lumbar spine, patients' age at first PAM administration, frequency of PAM administration, physical mobility, and the presence or absence of corrective osteotomy in the lower extremities.
Results
We found the prevalence of scoliosis to be 19% in 37 children with OI who underwent PAM therapy for a mean of 9.8 times, and the incidence of scoliosis were lower than has been reported in previous studies (39–100%) of patients who were not treated with BP. Sillence types III and IV and the presence of coronal vertebral deformity were significant risk factors for the development of scoliosis ($P = 0.03$). Starting BP therapy in early childhood prevented the occurrence and progression of scoliosis in children with types III and IV OI ($P = 0.03$).
Conclusions
This study suggest that BP decreases the incidence of vertebral deformity associated with bone fragility and subsequently decreases the incidence of occurrence and progression of scoliosis in children with OI, in particular those with type III or IV.
Disclosure
The authors declared no competing interests.

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P12

Elevated plasma c-terminal fibroblast growth factor, but not intact FGF23 or soluble Klotho, is associated with left ventricular hypertrophy in pediatric chronic hemodialysis patients

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Background
Cardiovascular disease is the leading cause of death in pediatric (ped) and adult ESRD patients. Left ventricular hypertrophy (LVH) is an independent predictor of mortality in ESRD. Besides traditional risk factors, such as high BP & fluid overload, high plasma FGF23 is associated with LVH in adult ESRD patients. Little is known about Kl, the renally produced cofactor of FGF23 for phosphorus (P) homeostasis. We studied ped HD patients for risk factors for LVH, including plasma FGF23 & soluble Klotho (sKl).
Methods
Cross-sectional study of 22 patients (16 males), 12–25 years old, HD 3 × per week, vintage 48 ± 34 m, spKt/V 1.6 ± 0.2; eight were anuric. BP & central BP (CBP, pulse wave tonometry) were obtained pre, intra and post-HD. ECHO for study was compared to ECHO within 1y; LVMI normalized for ht was used for LVH comparisons. Routine serum Ca, P, iPTH & 25OH-vit D were noted. Plasma c-terminal (c) FGF23, intact (i) FGF23 & sKl were measured by ELISA in patients; c-terminal fibroblast growth factor (cFGF23) & sKl were measured in 27 age-matched controls (ctl).

Results
cFGF23 was 1.3–2× higher than intact FGF23 (iFGF23) (cFGF23 100.919 RU/ml (IQR: 5.792; 315.934) vs iFGF23 75.520 pg/ml (2.734; 229.172) $P=0.03$) & positively (pos) correlated with iFGF23 ($r=0.9$, $P=0.00001$); both were much higher than cFGF23 for ctl (28 RU/ml (11; 45), $P=0.002$).sKl (557 pg/ml (412; 1072)) was no different vs ctl (685 (496, 1161), NS). Log cFGF23 & log iFGF23 pos correlated with serum P & Ca ($r=0.5$–0.6, $P<0.01$), negatively correlated with 25OH-vit D ($r=-0.4$, $P<0.05$) & were higher in anurics ($P=0.04$). Log cFGF23, but not log iFGF23 pos correlated with CBP & pre-HD systolic BP%ile for age/gender/ht ($r=0.4$, $P<0.05$). patients with log cFGF23 >50%ile from median had significantly elevated serum P, Ca, & LVMI (table; median (IQR)). patients with worsening LVMI from previous 1y had higher log cFGF23 (χ^2, $P=0.02$).

Table 1

Log cFGF23	Vintage m	Ca mg/dl	P mg/dl	iPTH pg/ml	25OH-Vit-D ng/ml	LVMI g/m$^{2.7}$	sKl pg/ml
<50%ile	32	9.25	5.1	343	27.5	34	972
$n=10$	(26.42)	(9.1,9.7)	(4.8,6.5)	(157,660)	(18.7,32.6)	(31,40)	(491,1090)
>50%ile	41	10.2	7.4	183	20.8	45	502
$n=12$	(22.86)	(10,10.8)	(6.7,8.1)	(150,417)	(15.5,31.6)	(40,53)	(393,673)
P value	NS	0.004	0.016	NS	NS	0.048	NS

Conclusion Compared to ctl, plasma FGF23 by either c or i method in ped HD patients is very high (>1000 fold) while sKl is no different. cFGF23 is significantly higher than and pos correlates with iFGF23. Not only Serum P pos but also serum Ca pos correlate with both cFGF23 and iFGF23, whereas higher cFGF23 was associated in this study with LVH (higher LVMI, worsening LVMI). Serum Ca in addition to P influences FGF23. FGF23 may be a ped HD cardiovascular risk factor, independent of sKl, but differences between cFGF23 and iFGF23 assay should be considered in future studies to be sure of CV risk categorization.
Disclosure
The authors declared no competing interests.
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P13

Galactosyltransferase-1 deficiency: a novel cause of bone fragility due to impaired proteoglycan synthesis
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Proteoglycans is a component of extracellular matrix, forming a mesh around structural proteins including collagen and elastin, and providing elasticity to tissue structure. Proteoglycans is formed by the attachment of glycosaminoglycans to a core protein, a process that requires three enzymes: galactosyltransferase-1, galactosyltransferase-2 and glucoronosyltransferase-1, encoded by *B4GALT7*, *B3GALT6* and *B3GAT3* respectively. *B3GALT6* mutations are associated with osteoporosis, but fractures have not previously been described in individuals with mutations in *B4GALT7*.
Male A presented at age 8 months with spontaneous rib fractures. He was born at term by elective caesarean section with no evidence of fractures at birth. Birth weight was 2.78 kg (−1.64 SDS). He developed severe gastrooesophageal reflux, faltering growth (length and weight −4.9 and −5.4 SDS respectively) and motor delay. His mother had multiple moderate impact fractures in childhood, but neither his father nor two half-siblings had fractured.
On examination, he was markedly hypotonic and unable to roll. He had little muscle bulk, but prominent subcutaneous fat. His sclerae were white. Other dysmorphic features included soft cleft palate, marked palgiocephaly and bilateral syndactyly of the second and third toes. A skeletal survey showed osteopenia, compression fractures of T12, L2 and L4 vertebrae and bilateral radioulnar synostosis. Novel compound heterozygous mutations in *B4GALT7 (*Cys214Tyr & 277dupC) were identified.
Prior to the genetic diagnosis, he commenced pamidronate at age 2.5 years due to increasing back pain requiring opioid analgesia and progression of vertebral collapse. After 1 year of treatment, improvement in pain and vertebral morphometry was evident. He has not sustained any long bone fractures.
Galactosyltransferase-1 deficiency is rare with only 26 previously reported cases. The phenotype is expanding, but common clinical features include short stature, hypermobility, and skeletal abnormalities including radioulnar synostosis. This is the first report of fractures in this disorder with multiple vertebral collapse fractures presenting prior to ambulation. Residual enzyme function varies by genotype, and it is postulated that these novel mutations might profoundly reduce galactosyltransferase-1 activity leading to the severe bone phenotype. This case highlights the need to consider defects of proteoglycans synthesis in individuals with fractures and short stature.
Disclosure
The authors declared no competing interests.
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P14

Accuracy of parental recall of children's lifetime fracture prevalence: implications for investigation of childhood osteoporosis
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Fractures are common in childhood, but multiple fractures during growth could indicate osteoporosis. Children with frequent fractures might benefit from further investigations for osteoporosis and as such, obtaining an accurate fracture history is important. The 2013 *International Society for Clinical Densitometry* Paediatric Osteoporosis Position Statement defined a clinically significant fracture history as two long bone fractures before age 10 years or three long bone fractures before 19 years of age, excluding fractures caused by high impact mechanisms. The accuracy of parental recall of their child's lifetime fractures has not previously been evaluated. We therefore assessed whether parental recall of lifetime fracture were in agreement with radiological reports obtained at the time of injury.
Parents of children (<18 years) attending the paediatric orthopaedic clinic following an acute musculoskeletal injury were invited to complete a written questionnaire on their child's fracture history, including age, site and mechanism of each previous fracture. Hospital records were reviewed to determine whether a fracture had been confirmed radiologically.
207 of 660 children (66% male, median age 11.8 years, range 1.2–17.3 years) reported a previous fracture (range 1–7). An injury treated at our hospital was identified in 214 of the 276 reported fractures, of which 34 (16%) had not resulted in a radiograph confirmed fracture. This was similar for reported upper (15%) and lower limb (20%) fractures ($P=0.51$).
For 150 children, all previously reported fracture episodes were managed at our hospital. Of these, 18 had a clinically significant lifetime fracture history on parental report alone. For two children (11%), the fracture histories were no longer considered clinically significant after review of radiology reports.
Approximately one in six previous fractures reported by parents to have occurred in their child's lifetime, had not resulted in a confirmed skeletal injury. Of those with an apparent clinically significant fracture history, one in nine children could have been investigated unnecessarily (e.g. vertebral radiographs, densitometry and/or blood sampling) when using only parental fracture reports. Parental recall of lifetime fracture history should be corroborated with radiological confirmation of skeletal injuries before undertaking extensive investigations for bone fragility in children.
Disclosure
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P15

Fibrous dysplasia in McCune Albright syndrome; treatment and follow up
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Aim
To evaluate the effect of bisphosphonate treatment in children with McCune Albright syndrome (MAS).

Materials and methods
Six MAS patients diagnosed between 1998–2012 with bone pain, bone fracture and bone deformity were evaluated retrospectively. Main outcome measures included disease presentation, diagnostic evaluation, management strategy, and outcome.
Results
The mean age of the patients were 16.5±8.2 years (four girls, two boys). The first signs has started at the age of 4.5±2.7 years and the patients were diagnosed at the age of 9.5±5.8 years. First patient admitted with recurrent fractures, the second and the sixth patients with deformities on the extremities, the fifth patient with bone pain, the third and fourth patients with early puberty and facial bone deformity. Bisphosphonate therapy was initiated at a dose of 20 mg/m^2 every 2 months. The mean serum levels of Ca, P, ALP, PTH, and osteocalcin were 9.9±0.8 mg/dl, 3.6±1 mg/dl, 368.8±175.6 IU/l, 35.3±1.6 pg/ml, 73.2±31.6 ng/ml respectively at the beginning of therapy. On the last evaluation the mean serum levels of Ca P; ALP; PTH; and osteocalcin were 9.2±0.3 mg/dl, 3.8±0.2 mg/dl, 418.3±427.9 IU/l, 47.2±22.5 pg/ml and 65.6±26.9 ng/ml retrospectively. The first patient who admitted with recurrent fractures had no fractures for four years and the dysplastic lesions did not progress. The third patient with cranial deformity the lesion progressed whereas in the other patient with cranial deformity the size of the lesion did not change.

Table 1

	Age	Duration of therapy (year)	Last visit age (year)	Height SDS beginning	Last visit height SDS	L1–L4 SDS	Last visit L1–L4 SDS
Case 1	15.6	4.0	30.0	−1.8	−1.98	−1.89	2
Case 2	3.4	7.0	13.3	−1.16	−1.84	−1.8	−0.16
Case 3	2.9	3.0	6.0	−0.27	0.85	1.3	1.85
Case 4	6.5	6.0	12.7	−2.63	−0.71	−1.1	−0.8
Case 5	12.4	0.5	16.3	−3.06	−2.44	−0.03	
Case 6	15.6	4.0	20.7	−1.41	−1.35	−0.42	−1.02

Conclusion
As a result, although bisphosphonate therapy in fibrous dysplasia improves bone mineral density, it has no effect on regression of the lesions.
Disclosure
The authors declared no competing interests.
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P16

Genotype in patients with osteogenesis imperfecta using a targeted exome sequencing: correlation with phenotype
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Objectives
Osteogenesis imperfecta (OI) is a relatively common skeletal dysplasia characterized by bone fragility, mainly resulting from mutations in the COL1A1 and COL1A2 genes. Phenotype–genotype correlation is not fully uncovered in OI. Additionally, more than ten genes have been found to be responsible for OI. In the current study, we determine mutations in patients with OI using a targeted exome sequencing and examine a phenotype–genotype correlation.
Methods
Twenty-two patients with OI clinically diagnosed were included in our study: type I, 13; III, 4; IV, 5. The medium age was 4.2 years; height SDS, −1.7; annualized fracture rate, 0.6; lumbar bone mineral density SDS, −2.9. A customized panel for the targeted exome sequencing constituted 34 genes associated bone strength, including 14 causative genes in OI. DNA from blood was subjected to the targeted exome sequencing, and variants were annotated. Sanger sequencing was carried out to confirm identified mutations and to determine regions uncovered or unread by the targeted exome sequencing. This study was approved by the IRB, and informed consents were obtained from patients and/or their guardians.
Results
Twelve mutations were found in the COL1A1 gene, whereas four in the COL1A2 gene. Other mutations were not confirmed in this study. Based on the types of mutations, non-sense mutations were detected in four patients; frameshift, 3; splice site, 4; glycine substitution, 5. Phenotypes were evaluated between glycine substitution mutations and non-functional mutations such as non-sense and frameshift. Annualized fracture rates were increased in patients with the glycine substitution mutations (4.7) compared to those with the non-functional ones (0.5). Patients with the glycine substitution (0.2 years) were younger than those with the non-functional mutations (4.7). All of the OI patients with the non-functional mutations were classified as type I and experienced no fetal bone deformities. Annualized fracture rates tended to be higher, but not significantly, in patients with the glycine substitution (0.5) than those with the non-functional mutations (0) during the year following the initiation of pamidronate treatment.
Conclusion
Phenotype and genotype are correlated in patients with OI to some extent. Further investigations are needed to fully uncover these correlations.
Disclosure
The authors declared no competing interests.
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P17

MRI features as surrogate markers of X-linked hypophosphatemic rickets activity
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Background and objectives
X-linked hypophosphatemic rickets (XLH) is the most common form of inheritable rickets. The treatment of rickets is monitored via laboratory tests such as alkaline phosphatase (ALP), clinical features, and plain X-rays. The objectives of this study were to describe the MRI features in XLH and to look for correlations between those features and XLH activity.
Study design
Twenty-seven patients (younger than 18 years with XLH due to a PHEX mutation) were included in this prospective single-center observational study. All patients consented to an MRI of the distal femur (frontal T1-weighted and 3D SPAIR sequences). XLH activity was assessed using height, leg bowing, dental abscess history and ALP. We looked for correlations between the MRI features and serum ALP and clinical features.
Results
The median maximum width of the physis was 5.6 mm (4.8–7.8), and 82% of the patients had a width >3 mm. The median transverse extent of the widening was 55% (42.9–66.2). Zone of provisional calcification appearance was abnormal on 21 MRIs (78%). Harris lines were present on 24 MRIs (89%). There were bone marrow signal abnormalities on 16 MRIs (59%), predominantly in the epiphysis (14 MRIs). Two patients (7%) presented with an osteochondritis. Serum ALP was correlated with the maximum physeal widening and with the transverse extent of the widening. There were no correlations between the clinical parameters and the MRI features.
Conclusion
MRI of the knee provides precise rickets patterns that are correlated with the biochemical marker of the disease.
Disclosure
The authors declared no competing interests.
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P18

A novel mutation in *CYP24A1* gene in an infant with severe hypercalcemia and unique neurological presentation
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Background
Loss of function mutations of *CYP24A1*, encoding vitamin D-24-hydroxylase, have been recently identified in idiopathic infantile hypercalcemia (IIH), a rare entity which may lead to severe complications.

Objective
We describe an infant with IHH due to a novel *CYP24A1* mutation and a unique neurological presentation.
Case presentation
The patient was born at term after normal pregnancy to healthy non-consanguineous parents. He presented at age 7 months with weakness, failure to gain weight, and developmental arrest in the preceding 2 months. Physical examination revealed pale, thin, apathetic infant with severe hypotonia and tonic upward gaze. Laboratory investigation revealed severe hypercalcemia of 20.3 mg/dl (normal 7.2–10), ionized calcium 2.7 mmol/l (normal 1.0–1.2), phosphate 3.8 mg/dl (normal 4.7–8.0), PTH < 3 pg/ml (normal 16–87), 25-hydroxy-vitamin D 53 ng/ml (normal 30–100), and 1,25-dihydroxy-vitamin D 92 pg/ml (normal 20–100). Urine calcium excretion was elevated, with calcium/creatinine ratio of 2.3 (normal for age < 0.8). Renal ultrasonography demonstrated normal-sized kidneys without nephrocalcinosis. After acute management with fluids, diuretics, pamidronate and calcitonin, calcium level decreased to 9.6 mg/dl, and the patient was discharged on low-calcium formula with no supplemental vitamin D. A month later, calcium level increased to 12.9 mg/dl and he received a second dose of pamidronate. Currently, the patient is 11 months old, with normal calcium level with no additional treatment; however, the neurological symptoms did not completely resolve.
DNA was extracted from whole blood and full sequencing of the coding regions of the *CYP24A1* gene was performed and revealed that the patient is a compound heterozygote of two mutations: E143del in exon 2 (a mutation that has been previously reported) and a novel truncating mutation in exon 8 (c.995_1001del-CAAACAG). Each parent carried one of the mutations.
Conclusion
This patient presents a case of severe hypercalcemia and to a novel *CYP24A1* mutation associated with neurologic deterioration and tonic upward gaze that have not been previously reported in IHH.
Disclosure
The authors declared no competing interests.
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P19

The role of body composition in the relationship between lifestyle factors and bone parameters of young children
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Objectives
Maximising peak bone mass (PBM) during growth is an essential part in the prevention of fractures and osteoporosis later in life. Two of the most important modifiable factors influencing PBM are diet and physical activity (PA). These factors can have either a direct or indirect effect on bone. For example, increasing PA would increase loads directly to the bone or cause muscle changes which would drive changes in bone. This study aimed to assess whether there was a direct association between lifestyle factors (dairy consumption, PA and sedentary behaviour (SB)) and bone size and density that was not explained by body composition.
Methods
Measurements of bone (pQCT), body composition (BodPod), food consumption and PA (accelerometry) were collected in 160 children (6–12 years). A novel statistical approach based on Sequences of Regressions, a subclass of Graphical Markov models, was used to investigate the role of lifestyle factors and body composition on bone outcomes.
Results
SB had a direct, inverse association with cross-sectional area (CSA) and vBMD at the distal tibia but not with diaphyseal parameters. No direct associations were found between vigorous PA (VPA) and bone parameters. However, VPA was associated with both lean mass (LM) and fat mass, which were directly associated with bone parameters. LM had a direct beneficial impact on all bone parameters, except cortical vBMD at the diaphyseal tibia. Dairy consumption was not associated with any outcome.
Conclusion
This paediatric study indicated that SB showed a direct inverse association with CSA at the distal tibia, whereas VPA was indirectly associated with bone outcomes via its association with body composition. This investigation contributes to the understanding of the role of SB and VPA in bone development which are important to consider when translating these findings into messages promoting healthy bone growth.
Disclosure
The authors declared no competing interests.
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P20

Bone mineral density in patients with autosomal recessive osteopetrosis after hematopoietic cell transplantation
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Objectives
Autosomal recessive osteopetrosis (OP) is a rare metabolic bone disease characterized by impaired osteoclast function resulting in defective bone resorption and generalized high bone mineral density (BMD). Excessive bone compromises bone marrow space, leading to marrow failure. The infantile malignant form is typically fatal within the first decade of life. The intermediate form presents later during childhood. Currently, the only potential curative therapy for OP is hematopoietic cell transplantation (HCT), which restores normal hematopoiesis and provides a source of functional donor-derived osteoclasts. Little is known about the effect of HCT on BMD in OP, particularly in intermediate form. The objective of this study was to examine long-term impact of HCT on BMD in patients with OP. We hypothesized that mean BMD *Z*-score will be lower in HCT recipients with malignant OP transplanted at a younger age than those with intermediate OP.
Methods
A cross-sectional study was conducted in five patients with OP (four males) transplanted at the University of Minnesota between 1995 and 2010. All patients received myeloablative conditioning. BMD *Z*-scores for L1–L4 (LBMD) and total body excluding head (TBMD) for patients < 18 years, were measured by dual energy X-ray absorptiometry.
Results
BMD data are shown in Table 1. Patients with malignant OP (transplanted at age ≤1 year) had mean LBMD *Z*-score −1.8±1.1 compared to LBMD *Z*-score 12.5±3.2 in patients with intermediate OP at a median of 4.3 years after HCT (range 3.1–19.1 years). TBMD *Z*-score was −0.7±0.5 for patients with malignant OP.

Table 1

Patient	1	2	3	4	5
Sex	M	F	M	M	M
Age at HCT (years)	0.2	0.5	1	24	33.2
Age at recent evaluation (years)	19.3	4.8	5.3	27.9	36.3
Height SDS at recent evaluation	−5.0	−2.4	−0.9	−1.4	−2.6
Pre-HCT LBMD *Z*-score	–	–	–	10.1	14.5
Post-HCT LBMD *Z*-score	−0.5	−2.2	−2.6	9.3	15.6
Post-HCT TBMD *Z*-score	−1.3	−0.4	−0.5	–	–

Conclusion
Patients with malignant OP who were transplanted during the first year of life had a normal or even low LBMD at most recent follow up versus patients with intermediate OP, transplanted during young adulthood, who had high LBMD. The clinical significance of this persistently elevated LBMD in patients with intermediate OP is unknown. Future studies should address the effect of HCT on bone quality and fracture risk in these patients.
Disclosure
The authors declared no competing interests.
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P21

Efficacy of GH therapy in short patients affected hypochondroplasia

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Since 1997, GH therapy has been approved for skeletal disorders including ACH and HCH patients in Japan. The efficacy of GH therapy for short period has been reported in several study. However, few study about efficacy and safety of GH therapy for long term have been shown. The aim of our study is to examine that GH therapy for HCH patients is efficient and safe enough and improve final height and proportion.

18HCH patients (11 males and seven females) who met the criteria for GH treatment initiation were entered in this study. An average age was 5.4 years. Initial height SDS was -3.57 ± 0.51 SDS. Mean GH treatment period was 6.3 ± 2.77 years. Height SDS, IGF1 value, height velocity (HV), upper and lower limb proportion rate, were retrospectively examined on the basis of medical records.

GH treatment itself improved height SDS from -3.57 ± 2.77 SDS to -2.95 ± 0.73 SDS. IGF1 level increased from -0.31 ± 1.2 SDS to $+1.02\pm1.4$ SDS after 1 year GH administration and kept above 0 SDS in all patients. As the result, HV remarkably changed from -2.18 ± 1.0 SDS to $+2.19\pm2.6$ SDS only 1 year treatment. After puberty, despite of GH treatment, height velocity fell down due to a lack of pubertal growth spurt.

In contrast, the longer GH treatment period showed better responses in an improvement of disproportion. There was no serious adverse effects related to GH treatment so far.

GH therapy for HCH can be effective in not only growth gain but also improvement of disproportion. The treatment effectiveness greatly differed in individuals as the phenotype widely varied. Especially, the period of GH therapy before puberty tends to improve height SDS. Therefore, the earlier GH therapy was introduced, the greater the effect was.

Disclosure

The authors declared no competing interests.

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P22

Racing to better bone health! A 6-month calcium and vitamin D randomised controlled trial in young male jockeys

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Objectives

Young male jockeys undertake calorie restriction and high volumes of physical activity during periods of musculoskeletal growth and development. Previous research shows that jockeys have compromised bone health[1–4] and display disordered eating[5–7]. Restricted intakes of calcium and vitamin D, together with excessive amounts of exercise, increase the risk of osteoporosis in males[8]. The aim of this study was to establish whether calcium and vitamin D supplementation would improve bone properties of young male jockeys.

Methods

We conducted a 6-month, randomised, double-blinded placebo-controlled trial with two groups of weight-, height- and age-matched apprentice male jockeys (age $=20.18\pm3.23$ years). Participants were supplemented with 800 mg of calcium and 400 IU of vitamin D ($n=8$) or a placebo ($n=9$) daily for 6-months. pQCT measured 4 and 66% distal tibia and distal radius bone properties at baseline and 6 months. Blood-borne markers of bone turnover, P1NP and CTX and vitamin D status were assessed.

Results

After co-varying for height, weight and baseline bone measurements, the supplemented group displayed greater post-intervention bone density at both the radius and tibia. At the tibia, greater bone density at the 66% proximal site for the supplemented group were observed in cortical content (mg$\times$mm) ($P=0.000$, partial $\eta^2=0.701$), cortical density (mg$\times$cm^2) ($P=0.001$, partial $\eta^2=0.592$), total area (mm^2) ($P=0.003$, partial $\eta^2=0.526$) and cortical area (mm^2) ($P=0.000$, partial $\eta^2=0.691$). At the radius, greater trabecular area (mm^2) ($P=0.028$, partial $\eta^2=0.341$) and cortical area (mm^2) 66% proximal site ($P=0.003$, partial $\eta^2=0.541$) were found in the supplemented group. No other between group differences were observed. Blood analysis indicated greater vitamin D (nmol/l) ($P=0.014$, partial $\eta^2=0.384$) and CTx (ng/l) ($P=0.011$, partial $\eta^2=0.400$) in the supplemented group.

Conclusions

This is the first randomised controlled trial to examine the efficacy of calcium and vitamin D supplementation in improving bone properties in a highly vulnerable, young athletic, weight-restricted population. Results indicate the beneficial effects of supplementation on bone properties in as little as 6 months. Whilst the study size is small, this intervention appears promising as a strategy for improving bone health in young athletes in weight-restricted sports.

References

1. Dolan E, *et al*. Weight regulation and bone mass: a comparison between professional jockeys, elite amateur boxers, and age, gender and BMI matched controls. *Journal of Bone and Mineral Metabolism* 2012 **30** (2) 164–170.
2. Dolan E, *et al*. An altered hormonal profile and elevated rate of bone loss are associated with low bone mass in professional horse-racing jockeys. *Journal of Bone and Mineral Metabolism* 2012 **30** (5) 534–542.
3. Greene DA, *et al*. Bone health of apprentice jockeys using peripheral quantitative computed tomography. *Int J Sports Med* 2013 **34** (EFirst) 688–694.
4. Waldron-Lynch F, *et al*. High bone turnover in Irish professional jockeys. *Osteoporosis International* 2010 **21** (3) 521–525.
5. Cotugna N, Snider OS & Windish J. Nutrition assessment of horse-racing athletes. *Journal of Community Health* 2011 **36** (2) 261–264.
6. Dolan E, *et al*. Nutritional, lifestyle, and weight control practices of professional jockeys. *Journal of Sports Sciences* 2011 **29** (8) 791–799.
7. Leydon M & Wall C. New Zealand Jockeys' dietary habits and their potential impact on health. *Int J Sport Nutr Exerc Metab* 2002 **12** (2) 220–237.
8. Ebeling PR. Osteoporosis in men. *New England Journal of Medicine* 2008 **358** (14) 1474–1482.

Disclosure

The authors declared no competing interests.

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P23

Relationship of IGF1 and bone parameters in 7–16 year old apparently healthy Indian children

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Objective

GH through IGF1 plays an important role in both bone growth and mineralization. This cross-sectional study was carried out to evaluate the relationship between serum IGF1 concentrations and dual energy X-ray (DXA) measured total body less head (TB) bone area (BA), lean body mass (LBM) and bone mineral content (BMC).

Methods

One hundred and nineteen children ($B=70$, age $=7.3$–15.6 years) were studied for their anthropometric parameters by standard methods and bone and body composition by DXA. Their fasting serum IGF1 concentrations were assessed by ELISA. IGF1 concentrations were converted to *Z*-scores. Bone and body composition parameters were also converted to *Z*-scores.

Results

Mean age of the boys and girls was similar (11.5 ± 1.8 years). Mean serum IGF1 concentrations and IGF1 *Z*-scores were similar ($P>0.1$) between boys and girls and were of the order of 302.3 ± 140.0, -1.37 ± 1.11 respectively. The TBLBM for age and TBBA for age *Z*-scores were significantly greater ($P<0.05$) in

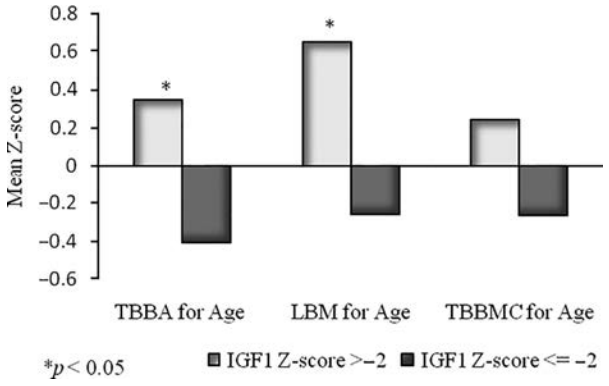

Figure 1 Mean TBBA, LBM and TBBMC *Z*-scores in children with IGFIZ-score below and above-2.

children with IGF1 Z-score >-2 than children with IGF Z=score <-2. (TBLBM Z-score: 0.34 ± 0.8, -0.4 ± 0.9; TBBA Z-score: 0.64 ± 0.9, -0.25 ± 1.0). The mean total body bone mineral content for age Z-scores were 0.24 ± 0.9 and -0.26 ± 0.9 in children with above and below -2 of IGF Z-score ($P>0.1$).
Conclusion
Serum IGF1 concentrations were more strongly associated with BA and LBM (Fig. 1), suggesting that its effect on bone is greater with respect to periosteal bone acquisition and through its effect on muscle mass.
Disclosure
The authors declared no competing interests.
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P24

Bone status of Indian children and adolescents with type 1 diabetes mellitus

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Objective
Aim was to cross sectionally study bone health parameters assessed by DEXA and serum IGF1 concentrations in 6–16 year old children with type 1 diabetes. We hypothesized that height and bone parameters would be impaired in diabetic children compared with contemporary reference population.
Method
Bone mineral content for total body (less head) (TBBMC) and lumbar spine was measured by DXA ($n=170$, 77 boys). Z-scores for TBBMC for bone area (TBBA), and lumbar spine bone mineral apparent density (LSBMAD) were computed (Bone 2011;48:810-9). Height was measured and converted to Z-score (HAZ). Serum IGF1 concentrations were measured by ELISA.
Result
Mean age was 11.1 ± 3.8 years, duration of diabetes was 2.2 ± 2.5 years and HbA1c was $10.1\pm1.8\%$. Diabetic children were shorter and lighter than reference population (HAZ -0.6 ± 1.1 and WAZ -0.6 ± 1.0); Z-scores for HAZ and TBBA for height were <-2SD in 12 and 6% respectively. Duration of diabetes ($\beta=-0.180$, $P=0.000$) and metabolic control (HbA1c; $\beta=-0.096$, $P=0.052$) were significant negative predictors of HAZ and TBBA for height Z. Using the Molgaard *et al.* (Archives of Disease in Childhood. 1997;76:9–15) approach, children with longer duration of diabetes had lower HAZ (-0.31 ± 0.92 vs -1.28 ± 1.11; $P=0.000$; 'short bones') and TBBA for height Z-scores (0.12 ± 1.62 vs -0.53 ± 0.94; $P=0.054$; 'slender bones'). However, the TBBMC for TBBA Z-scores were not significantly affected (-0.12 ± 1.17 vs 0.21 ± 1.32; $P>0.05$); thus children did not have 'light bones'. Serum IGF1 Z-scores were lower amongst the group with longer disease duration (-1.58 ± 1.3 vs -2.63 ± 0.7; $P=0.037$).

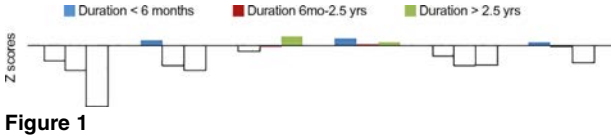

Figure 1

Conclusion
Longer duration of diabetes was associated with shorter and slender but appropriately mineralized bones. Small and slender bones in diabetic children may increase risk of fragility fractures in future.
Disclosure
The authors declared no competing interests.
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P25

Sitting time has a stronger effect on bone than moderate plus vigorous activity

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Objective
The use of high-impact weight bearing physical activities has been accepted as a means to increase osteogenic effects on bone. Studies in adolescents found that physical activity could counteract the detrimental effects on bone associated with television time in boys and time spent studying in girls. Our aim was to test the effects of the percent of time spent in moderate plus vigorous activities (ModVig) and sitting (SIT) on bone health. We hypothesized that high ModVig would increase bone size and strength and offset the detrimental bone effects of high SIT.
Methods
This cross-sectional study included 159 (83 males) children aged 6–18 years (mean 9.6 ± 2.7). Periosteal (PeriC) and endosteal (EndoC) circumference, cortical thickness (CrtThk) and bone strength (pSSI) of the distal tibia were measured using pQCT. Bone mineral content (BMC) of the hip, femoral neck (FN), spine and whole body were measured by DXA. ModVig and SIT were obtained by questionnaire. Regression analyses controlling for age, sex, age-by-sex, height and weight were used to test effects of ModVig and SIT on bone outcomes.
Results
ModVig was not associated with any DXA measures. Higher percent ModVig lead to a smaller EndoC ($P=0.01$) with no changes in other pQCT measures. On the other hand, children with higher SIT had smaller PeriC and EndoC, which lead to a lower pSSI than children who sat less ($P\leq0.02$, all) despite a greater CrtThk with higher SIT ($P=0.03$). Children with high SIT also had lower hip BMC ($P=0.01$).
Conclusions
Children with higher percent of time spent sitting had smaller and weaker bones in the lower leg and had lower hip BMC than children who sat less. Time spent in moderate to vigorous activity did not offset these negative outcomes. Public health messaging aimed at decreasing sitting time in addition to increasing moderate plus vigorous activity may have more of a beneficial effect on improving pediatric bone health.
Disclosure
The authors declared no competing interests.
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P26

Effects of running bike use on bone quality in non-ambulant children with cerebral palsy: a pilot study

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Children with cerebral palsy who are unable to walk independently are prone to lower limb muscle weakness which contributes to pain, deformity and functional loss. As a result of these motor difficulties the children are less physically active than their unimpaired peers and subsequently at greater risk of reduced bone density. This pilot study introduced a novel mobility device, running bikes, to a group of non-ambulant children with cerebral palsy to investigate if it was a feasible mode of weight-bearing exercise.
Fifteen children with cerebral palsy aged 4–12 years were recruited from two specialist schools. All children were unable to walk independently, with Gross Motor Function Classification System Levels IV $n=10$ and V $n=5$). The children used the running-bikes in their specialist schools three times weekly for 12 weeks, assisted by their physiotherapists. Ability to use the running bike and bone quality was assessed pre and post intervention. Bone quality was assessed by quantitative ultrasound (QUS) technique of the calcaneus (Sonost-3000). The main values of QUS are speed of sound (SoS m/s), broadband attenuation (dB/MHz) and bone quality index (BQI).
Ability to use the running bike significantly improved over the 12 weeks ($P=0.000$). The mean distance travelled per session increased from 51m pre-intervention to 123m post-intervention. The mean pre-intervention QUS scores for the left limb were: BUA 49.2; SOS 1504.24; BQI 58.2. The mean post-intervention QUS scores were BUA 52.0, SOS 1510.4; BQI 63.8. Paired *t*-test showed a significant difference between the BQI scores $P=0.037$, whilst no significant difference was found for the BUA ($P=0.24$) or SOS scores ($P=0.12$). This pilot study has shown that despite their level of disability, running bikes are a feasible mode of exercise for this group of children. This study was not powered to show significant changes in bone quality. Despite this the QUS data showed positive signs of improvement over the short follow up period which is encouraging. Further studies are needed to elucidate the role of running bike use on bone strength in non-ambulant children with cerebral palsy.
This study was funded by Sparks, the children's medical research charity.
Disclosure
The authors declared no competing interests.
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P27

Bone mineral density and clinical outcome after intravenous bisphosphonate discontinuation in children with osteogenesis imperfecta

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Objectives
i) To evaluate the bone mineral density (BMD), and clinical outcomes of intravenous bisphosphonate treatment (IVT) and after treatment discontinuation in children with osteogenesis imperfecta (OI). ii) To compare the clinical outcome of those who discontinued IVT and those who had progressed from IVT to maintenance oral bisphosphonate therapy.
Methods
A retrospective study was conducted on 28 children with OI who had discontinued IVT (21 pamidronate and seven zoledronic acid). Data were collected at four time points: before treatment, before IVT discontinuation (IVD), 1 and 2 years after IVD. 21 patients (baseline mean age 5.2±3.7 years) were off therapy completely after IVD (group 1); seven patients (mean age 5.8±4.5) were switched to maintenance oral bisphosphonates (risedronate or alendronate) after IVD (group 2).
Results
Duration and number of IV infusions were similar in both groups (Group 1: 3.8± 2.9 years, 11±8.0 infusions; Group 2: 3.93±2.4 years, 11±5 infusions). Lumbar BMD (LBMD) and total bone mineral content z-scores in all patients increased significantly from baseline to before IVD and were maintained for 2 years after IVD. There were no significant differences in LBMD z-scores, and the change in BMD parameters from before and 2 years after IVD between two groups. The fracture rates significantly reduced during the treatment, and increased slightly after IVD in both groups. In Group 1, height z-scores were preserved at 2 years after IVD. The rate of LBMD change from 1 to 2 years after IVD was positively correlated with duration of treatment ($P=0.01$) and number of infusions ($P=0.03$). Patients aged <5 years consistently had significantly higher LBMD z-scores over time compared to those >5 years ($P=0.01$).
Conclusions
IV bisphosphonate therapy significantly increased BMD and reduced fracture rate during the treatment. The beneficial effect in BMD was maintained for 2 years after discontinuation of IV therapy, with results as good as those switching to oral therapy. Younger age at the start of therapy, with longer duration and higher number of infusions was associated with greater BMD outcome after treatment discontinuation.
Disclosure
The authors declared no competing interests.

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P28

Year-round cord blood vitamin D concentrations in women from diverse ethnical backgrounds in a Mediterranean area in Spain

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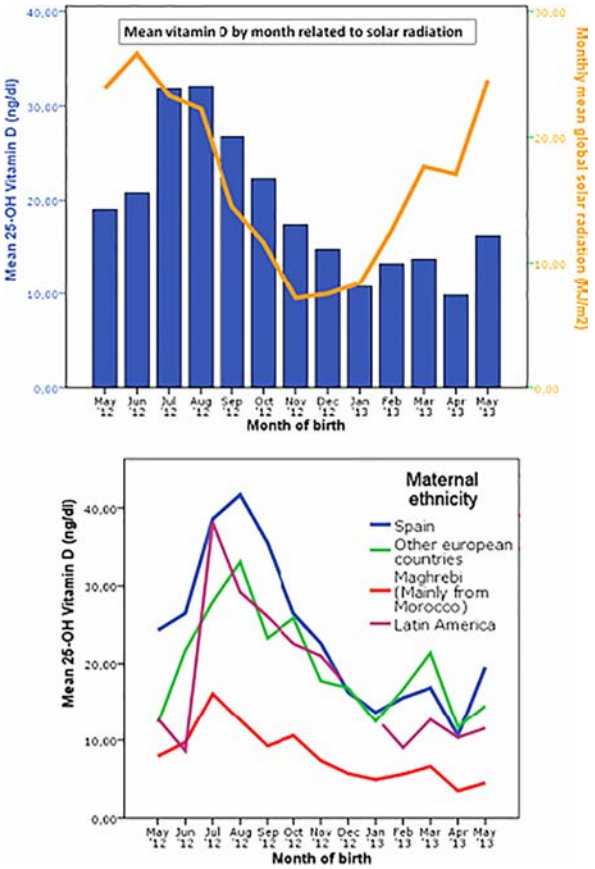
Background
Vitamin D (Vit-D) plays a role in calcium metabolism during pregnancy, and studies have found widespread deficiency in this period. Its significance is still not fully understood, although low Vit-D levels have been associated with increased risk for preeclampsia, bacterial vaginosis, neonatal sepsis and early respiratory infections in the infant. Supplementation to the pregnant mother remains a matter of debate; thus, it is important to better understand the causes, risk factors for and possible consequences of the deficiency.
Objective and hypotheses
To ascertain cord blood Vit-D levels and some potential risk factors for the deficiency in a coastal Mediterranean climate region.
Method
The study was conducted between May 2012 and May 2013 in the Baix Penedes County Hospital (El Vendrell). We measured the Vit-D levels of 358 cord blood samples from 47% of neonates born in the hospital during the study period. Mothers were 57% of Spanish origin, 25% Moroccan, 10% LatinAmerican and 8% from other European countries. Vit-D in cord blood was measured at birth and information collected on the mothers throughout pregnancy and their offspring at birth.
Results
Vit-D levels in all groups closely followed the solar radiation pattern during the year with the highest being in August and the lowest in January. However, mothers of Maghrebi origin had the lowest levels on average (9.2 ng/dl) which were consistently low during the year and almost undetectable in winter months (see Figure 1). Mean Vit-D levels had a positive relationship with Vit-D-containing supplements, and a negative relationship with weight gain during pregnancy and heavy tobacco consumption.



Conclusion
Significant differences were observed in this population among seasons and ethnic groups, with certain relationships to risk factors for Vit-D deficiency.
Disclosure
The authors declared no competing interests.

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P29

Type 1 diabetes mellitus may predispose to lower bone mineral density through lower osteoblast signaling from increased levels of Dickkopf-1

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Background
Several bone metabolic pathways are disrupted in diabetes mellitus (DM), leading to reduced bone mass. Increased fracture risk and elevated Dickkopf-1, which is

an inhibitor of the Wnt/b-catenin bone metabolic pathway, have been documented in adult patients with type 2 DM. No relevant data exist on childhood type 1 DM (T1DM).
Objective and hypotheses
We aimed at studying plasma Dickkopf-1 concentration in children and adolescents with T1DM and controls. We subsequently correlated Dickkopf-1 levels with metabolic bone markers and bone mineral density (BMD).
Methods
We evaluated 40 children and adolescents with T1DM (mean ± s.d. age: 13.04 ± 3.53 years,T1DM duration: 5.15 ± 3.33 years), along with 40 healthy matched controls (age: 12.99 ± 3.3 years). Serum Dickkopf-1, Sclerostin, Osteocalcin, C-telopeptide crosslinks (CTX), electrolytes, PTH, total 25(OH) D were measured and lumbar spine and total body BMD were evaluated.
Results
BMD was found lower and Dickkopf-1 levels were found higher (13.56 ± 5.34 vs 11.35 ± 3.76 pmol/l, $P = 0.0194$) in T1DM patients. A trend for lower values was found in girls (13.36 ± 4.04 vs 11.72 ± 5.14 pmol/l, $P = 0.06$) and in pubertal children (13.61 ± 4.87 vs 11.83 ± 4.56 pmol/l, $P = 0.054$). Dickkopf-1 correlated with Sclerostin and L1–L4 BMD z-score only in controls and with Osteoprotegerin and i-Phosphorus only in patients, while in both groups a significant correlation with log (CTX) and √ALP was documented. A significant correlation of Dickkopf-1 with IGF1 and insulin dose was also found in patients.
Conclusion
Higher levels of Dickkopf-1 were found in T1DM children and adolescents, indicating a down-regulated Wnt signaling system and possible lower osteoblast activation that could be associated with T1DM osteopathy.
Disclosure
The authors declared no competing interests.
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P30

Whole-body MR imaging as diagnostic tool in children with hereditary multiple osteochondromas

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Patients with hereditary multiple osteochondromas (HMO) undergo frequent X-rays to evaluate the growth of the osteochondromas. The conventional radiographs show clear images of the growth of the bony part of the osteochondromas and of the growth direction of the long bones. However the cartilage cap on the osteochondroma nor the cartilage of the nearby epiphysis or the surrounding soft tissue of the osteochondromas is shown. Besides these disadvantages taking frequent radiographs carries the potential risk of inducing malignant degeneration trough radiation.
In this study we look at the use of whole-body (Wb) MR imaging as a tool to follow patients with HMO.
Two HMO affected children underwent two whole-body MRI's in a year time to identify the osteochondromas and to follow their growth. The MR images were compared to regular follow-up radiographs of these patients during this year.
All the known osteochondromas found on the radiographs of the extremities were visible on the Wb MRI. At least one osteochondroma was seen on the Wb MRI earlier than detection was possible on the x-rays. When comparing the visibility of the different Wb MRI settings, the proton density spir setting of the Wb MRI makes the osteochondromas best visible.
Whole-body MRI is an effective tool to follow patients with HMO, with the disadvantage that sometimes general anaesthesia is needed to preform the scan. The surrounding soft tissue and the cartilage cap of the osteochondroma are clearly visible.
Disclosure
The authors declared no competing interests.
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P31

Mineral metabolism in children with autosomal dominant polycystic kidney disease

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic cause of renal failure. Data from adult ADPKD population show increased fibroblast growth factor 23 (FGF23) levels while circulating Klotho levels decrease, with a low TmP/GFR even in patients with normal renal function. Moreover, in ADPKD animal models, cyst lining renal cells were demonstrated to produce FGF23, although the animals displayed FGF23 resistance. No data are available in a paediatric ADPKD population. In this multicentre study, we prospectively assessed bone metabolism and renal phosphate handling in children with ADPKD and normal renal function by analysing blood and urine parameters. Based on normal values according to age, we made percentile (P) charts for serum phosphate and TmP/GFR. Hypophosphatemia and urinary phosphate wasting were defined as values ≤P5. We included 119 ADPKD patients (67 males, median (range) age 10.5 (0.5–18.6) years). PTH levels were in the normal range, 45% of children displayed vitamin D deficiency. Hypophosphatemia and urinary phosphate wasting were observed in 11, and 27% of the children respectively (Figure 1). This is the first report highlighting hypophosphatemia in combination with renal phosphate leak in ADPKD children with normal eGFR. Our results confirm recent data in adult ADPKD patients and point to an abnormal FGF23 metabolism starting at paediatric age. Further studies are required to elucidate the underlying pathophysiology and to investigate potential clinical consequences.
Stéphanie De Rechter, Djalila Mekahli and Elena Levtchenko are supported by the Fund for Scientific Research, Flanders.

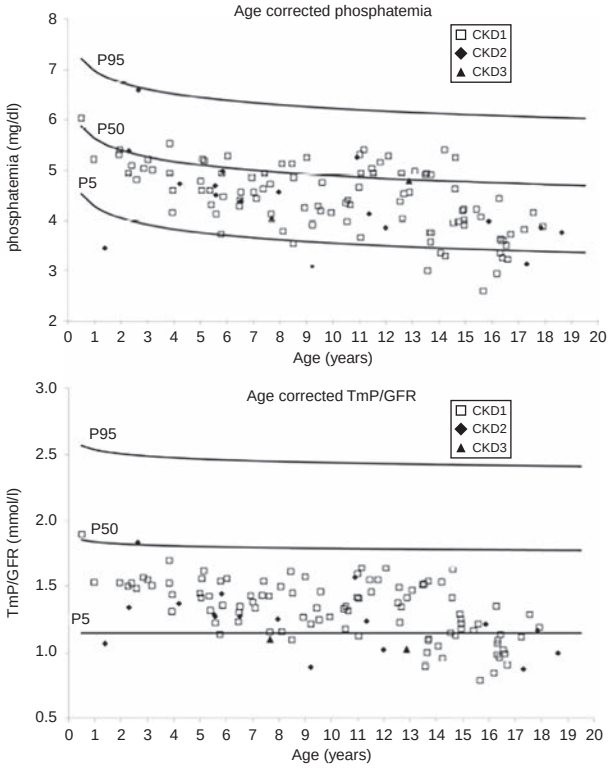

Figure 1

Disclosure
The authors declared no competing interests.
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P32

Characteristics of Malawian children undergoing corrective bone surgeries of rickets-like lower limb deformities

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Cases of non-vitamin D deficiency rickets have been reported in African countries including The Gambia, South Africa and Nigeria where the likely aetiology is a chronically low dietary calcium intake. Additional aetiological factors in Gambian studies are iron deficiency leading to a disruption in phosphate metabolism.

Surgical correction of pathological rickets-like lower-limb deformities is the most common operation performed at the Beit Cure Orthopaedic Hospital in Blantyre, Malawi. During 2008–2009, 81 cases were enrolled in a surgical intervention study. The aim of this present study was to identify the characteristics and aetiology of pathological bow-leg (**BL**, $n=44$) and knock-knee deformities (**KK**, $n=37$) and to identify similarities with previously described African cohorts.

Whole blood was analysed for malaria parasite ($n=1$, positive) and serum for 25-hydroxyvitamin D (25OHD, DiaSorin, USA), calcium (Ca), phosphate (Phos), ferritin (Ferr), C-reactive protein (CRP) and total alkaline phosphatase (TALP)(Koni Analyzer,Finland).

At first presentation, children with **BL** were younger (mean (s.d.) 4.5(2.1) vs 6.7(3.9) years, $P=0.002$), and tended to start walking 2 months earlier than **KK** ($P=0.1$). 25% of **BL** and 32% of **KK** had family members with rickets-like deformities. In the children, the mean angle of deformity did not differ between the groups (**BL**: 29(9) vs **KK** 30(9) degrees, $P=0.8$). Mean 25OHD was 65(21.4) nmol/l ($n=0<25$ nmol/l, $n=18<50$ nmol/l) and tended to be higher in **KK** (25OHD **BL**: 61.1(23.7) vs **KK**: 69.7(17.8), $P=0.08$). 12% of children had low iron stores (Ferr <15 µg/l) and 44% had a degree of inflammation (CRP >10 mg/l). TALP (25% >215 RU/ml), Phos (14% <1.45 mmo/l) and Ca (12% <2.20 mmol/l) did not differ between groups or by angle of deformity with the exception of Phos which was negatively associated with angle of deformity (β-coefficient (SE) $-0.006(0.003)$ mmol/l, $r^2=4.1\%$, $P=0.05$. Phos was the strongest negative predictor of TALP (β(SE) $-196(47)$ U/l, $r^2=21.1\%$, $P=0.0001$).

In Malawi, children with **BL** are younger than those presenting with **KK.** As in The Gambia, rickets-like deformities in Malawi are more common in boys (75%) than girls (25%) and are unlikely to be caused by vitamin D deficiency. The inverse relationship between Phos with TALP and angle of deformity may suggest a disruption in phosphate metabolism.

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Disclosure

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P33

In utero effects of iron status on infant fibroblast growth factor-23 and mineral metabolism

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Fibroblast growth factor-23 (FGF23) is a bone derived phosphate-regulating hormone which is elevated in hypophosphataemic rickets. Recent findings demonstrate iron deficiency as a potential mediator of FGF23 expression and murine studies have shown *in utero* effects of maternal iron deficiency leading to increased FGF23 concentration and disordered bone development (Clinkenbeard. JBMR 2013). Children with rickets in rural Gambia, West Africa, have high prevalences of iron deficiency and elevated FGF23. The aim of this study was to elucidate potential *in utero* effects of iron status on infant FGF23 and mineral metabolism as potential antecedents of rickets in The Gambia.

Infants born to mothers with normal (**NI** $n=25$) and low (**LI** $n=25$) iron status during pregnancy, from a Gambian mother-infant trial ISRCTN49285450 had blood and plasma samples analysed at 12, 24, 52, 78 and 104 weeks of life for circulating haemoglobin (Hb), C-terminal (C-FGF23; Immutopics, USA) and intact-FGF23 (I-FGF23; Kainos, Japan), phosphate (Phos), total alkaline phosphatase (TALP) and cystatin C (Cys C) (Kone Analyser 20i, Finland).

Circulating I-FGF23, Phos, TALP and Hb decreased and estimated glomerular filtration rate (eGFR; 74.835/(cys C (mg/l)^1.333) increased over time (mean(s.d.) I-FGF23: 49.1(13.1) to 34.3 (10.9) pg/ml, Phos: 1.86(0.13) to 1.69(0.17) mmol/l, TALP: 406(133) to 318(135) U/l, Hb: 10.7(1.6) to 9.4(1.6) g/dl and eGFR: 59.9(11.2) to 94.5(23.4) ml/min. All $P\leq0.0001$)). C-FGF23 did not change significantly over-time (402(218) to 487(502) RU/ml, $P=0.15$). C-FGF23 and TALP were significantly higher in **LI** compared with **NI** from 52 week and from 24 week for TALP. Adjusted for timepoint Hb was the strongest negative predictor of C-FGF23 concentration (Beta coefficient (SE) $-104.1(27.28)$ RU/ml, $P\leq0.0002$; group difference $P=0.03$) and Phos the strongest positive predictor of I-FGF23 (31.4(3.9) pg/ml, $P\leq0.0001$, group difference $P=0.8$) and I-FGF23 did not predict C-FGF23 ($-2.68(3.56)$ RU/ml, $P=0.45$, group difference $P=0.03$).

In conclusion, this study suggests that poor maternal iron status is associated with an increased infant C-FGF23 and TALP concentration in humans. Further studies are required to investigate the role of maternal iron status in the regulation of offspring FGF23 and mineral metabolism as antecedents of rickets.

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Disclosure

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P34

Abstract withdrawn.

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P35

Spinal muscular atrophy: another non-ambulatory population at risk for low bone mineral density

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In children with spinal muscular atrophy (SMA): i) describe bone mineral density (BMD) measured by dual-energy x-ray absorptiometry (DXA); ii) examine bone health factors; iii) examine change in BMD over time and pamidronate effect.

DXA results, medications, ambulation, 25-OH-Vit D levels, and fracture history were retrospectively reviewed in 14 children (five girls) with SMA. Sites scanned included whole body (WB), lumbar spine (LS), and lateral distal femur (LDF). Age and gender-matched *z*-scores were calculated.

There were nine type I, four type II and one type III SMA patients with a mean age of 9.9 years (range 3.1–18.5) at the initial DXA scan. Five subjects had serial DXA studies, including two treated with pamidronate. Thirteen patients were non-ambulatory; the type III patient used a walker.

LDF DXA was obtained on all subjects. Mean (range) LDF BMD *z*-scores were: R1 -9.0 (-3.1 to -18.5); R2: -6.6 (-3.8 to -14.3) R3: -5.6 (-2.7 to -12.6). Only six LS and four WB measurements could be obtained due to scan artifacts. Average LS (-2.2 (0.8 to -2.7)) and WB (-2.5 (-1.2 to -3.8)) BMD *z*-scores were higher than LDF scores. The type III patient had normal LS and WB BMD but low LDF values. Five patients had history of fracture (three non-traumatic, two with multiple fractures received pamidronate). Available 25-OH-Vit D levels at the time of initial DXA ($n=4$) ranged from 23 to 40.1 ng/dl, with median level of 30.5.

Serial scans

Length of observation ranged from 2 to 4 years in two treated patients and from 0.7 to 3.7 years in three untreated patients. Both treated patients had SMA type I and fractured young (ages 1 and 3 years). As expected, their *z*-scores increased dramatically with pamidronate. BMD remained low over time in the untreated patients.

Children with SMA have below normal BMD, particularly of the lower extremities. Two patients who suffered multiple non-traumatic fractures and received bisphosphonate saw improved BMD and have not fractured since treatment began. The LDF proved to be the most accessible DXA site to measure in children with SMA.

Disclosure

The authors declared no competing interests.

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P36

Bone mineral density, pubertal status and ability to walk are associated to fracture incidence in patients with Rett syndrome

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Rett (RTT) syndrome is a neurodevelopmental disorder that affects girls almost exclusively. The majority are related to mutations in the MECP2 gene.
Patients with RTT syndrome have a high incidence of fractures that can occur at a young age. One of the objectives of this study was to identify clinical, radiographic and biological parameters associated to fracture incidence.
89 RTT patients bearing a *MECP2* mutation who had no past history of bisphosphonate treatment or orthopedic surgery to the spine were recruited prospectively. The following clinical, radiographic and biological parameters were evaluated: history of fractures and anti-epileptic drugs, ability to walk, BMI, pubertal status, Kerr severity score, daily calorie, calcium and vitamin D intake, bone mineral density (BMD) at the spine and hip using DEXA, X-rays of the spine and urinary calcium excretion.
Mean age of patients was 11.8±7.1 years 19/89 (21%) of patients had a history of fracture(s). Ambulatory patients had a higher incidence of fractures (41%) compared to those unable to walk (14%) even though they had a higher BMD of −1.72±0.18 *z*-score SDS at the spine and −2.48±0.23 *z*-score SDS at hip compared to −3±0.23 and −2.48±0.23 respectively, in non-walking RTT patients. Even though pubertal patients had a higher BMD compared to non-pubertal patients, −1.6±0.33 vs −2.27±0.15 *z*-score SDS at the spine, the incidence of fractures was the highest (30%) in the pubertal ambulatory patients. BMD at the spine and the hip was significantly lower in patients who had fractures, respectively at −2.78±0.3 and −3.21±0.36 SDS *z*-score compared to patients with no history of fractures, respectively at −1.76±0.16 and −2.24±0.18 SDS *z*-score. No difference was found for the other studied parameters between the fractured and non-fractured patients. BMD was significantly correlated to the disease severity Kerr score and BMI *z*-score.
Pubertal ambulatory RTT patients have the highest incidence of fractures.
BMD, ambulatory status and pubertal development are related to fracture incidence in RTT patients.
Disclosure
The authors declared no competing interests.

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P37

Teriparatide following bisphosphonates in the treatment of osteoporosis in post-pubertal teenagers

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Background
Treatment of osteoporosis with bisphosphonates may result in severe suppression of bone turnover leading to adynamic bone disease. Teriparatide is now commonly used as an anabolic agent in adults with osteoporosis, and has the potential to reverse the effect of bisphosphonates. However its use in pediatrics is restricted to those with closed growth plates and information regarding its effect in this age group limited.
Objective
To study the effect and safety of teriparatide in post-pubertal teenagers and very young adults who previously were treated with bisphosphonates for their osteoporosis and developed adynamic bone disease.
Patients and methods
Seven post-pubertal patients with osteoporosis who were previously treated with bisphosphonates and developed evidence of adynamic bone disease manifested by very suppressed bone turnover markers, were treated with teriparatide 20 µ per day for 2 years. The incidence of fragile fractures in the 2 preceding years and during the treatment period were compared, as were spinal DXA, serum creatinine, Ca, P, PTH, bone specific alkaline phosphatase (BSAP), osteocalcin and urine NTX.
Results
Patients age ranged between 16 and 23 years, mean±S.D. 18.7±2.4, 5 were female. In all patients pre-treatment radiographs showed closure of growth plates. With treatment the incidence of fragile fractures decreased from 0.21 to 0.00 year (NS). Spinal *z*-scores improved from −4.49±1.20 to −3.71±0.91 ($P<0.005$). Serum creatine, Ca, P and did not change significantly, staying within normal range in all, besides one patient who developed transient mild hypercalcemia at 11.2 mg/dl. BSAP increased from 22.5±7.7 to 43.5±17.1 µ/l ($P<0.02$), osteocalcin from 17.8±3.3 to 57.1±30.9 ng/ml ($P<0.05$) and urine NTX from 59.4±18.0 to 217.5±113.3 nmol/mmol creatinine ($P<0.05$). No patient developed adverse effects requiring discontinuation of the medicine.
Conclusion
In this small sample of patients teriparatide proved itself to be safe and effective treatment in reversing adynamic bone disease and improving its condition. Further studies are warranted on the use of this anabolic agent in the pediatric age group.
Disclosure
The authors declared no competing interests.

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P38

Serum 25-vitamin D level is lower in African American compared to Caucasian children

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Background and Objective
Serum 25-Vitamin D level (S-VitD) was recently reported to be significantly lower in African American (AA) adults compared with their Caucasian (CS) counterparts, despite having a higher bone mineral density, due to lower serum vitamin D-binding protein (NEJM 2013; 369: 1991). The objective of this study was to examine if this observation holds true in Hispanic and AA children.
Material and methods
The database of clinical laboratory from a tertiary level children's hospital was analyzed from January 2012 to December 2013 for S-VitD, S-PTH and serum creatinine (S-Cr). The data was included for analysis only if all the measurements were done on the same blood sample. Only the initial sample on a given child was included in the analysis. S-VitD was measured by tandem mass spectrometry on AB4000 QTrap with RR of >30–100 ng/ml. S-PTH was measured by an immunoassay (Immulite™) with RR of 7–75 pg/ml. S-Cr was measured by an enzymatic assay on Vitros autoanalyzer. The reference range is age based but a cut-off value of <0.6 mg/dl will be normal across the whole pediatric age group. We included S-VitD for children with S-Cr <0.6 mg/dl and S-PTH <250 pg/ml to exclude children with primary hyperparathyroidism, pseudohypoparathyroidism and chronic kidney disease. The SPSS 20 was used for statistical analysis.
Results
The database identified 596 samples (CS=493, AA=54, Hispanic=49) with S-Cr <0.6 mg/dl and S-PTH <250 pg/ml. The mean+S.D. for S-VitD and S-PTH were 35.8±13.7 ng/ml and 38.7±30.4 pg/ml respectively. On univariate analysis S-VitD in AA 30.7±13.5 ng/ml was lower vs CS 37.0±13.5 ($P=0.001$), and P=NS vs Hispanic children 33.8±14.5, with no difference between CS and Hispanics. There was no statistical difference for S-PTH and S-Cr between the three groups. The boxplot distribution for S-VitD by race is shown in Figure 1. The analysis for children with S-Cr <1.0 mg/dl ($n=839$) yielded similar results (data not shown).

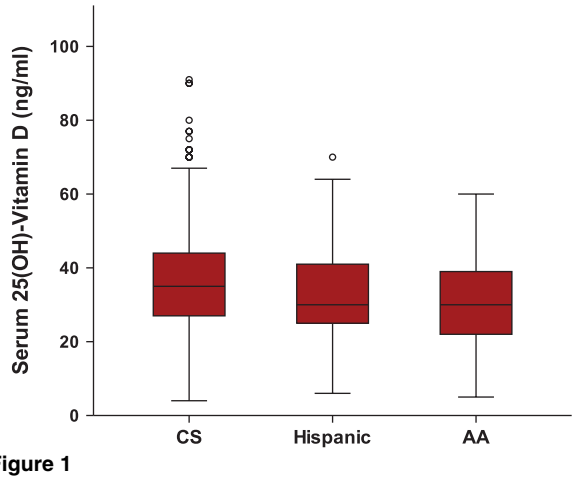

Figure 1

Conclusions
AA children have significantly lower S-VitD levels compared to CS children with similar S-PTH levels. A comprehensive prospective analysis is needed to validate these findings and develop a robust assay for bioavailable S-VitD in children across different ethnicities.
Disclosure
The authors declared no competing interests.
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P39

Fracture and bone mineral density outcomes after bisphosphonate discontinuation in children with osteogenesis imperfecta treated with zoledronic acid compared to pamidronate

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Objectives
Cyclical intravenous pamidronate (PAM) and zoledronic acid (ZOL) increases bone mineral density (BMD) and reduces fractures in children with osteogenesis imperfecta (OI). The aims of this study were to evaluate fracture and BMD outcomes after treatment discontinuation in children with OI treated with ZOL compared to PAM.
Methods
21 patients (mean age 5.1 ± 3.8 years) received PAM (1 mg/kg per day x 3 days q 3 months for the first year). Seven patients (mean age 6 ± 4.3 years) received ZOL (0.025 mg/kg/dose q 3 months for the first year). Frequency of infusions was decreased in subsequent years. Fractures and lumbar BMD (LBMD) z-scores were assessed at four time points: before treatment, before treatment discontinuation, 1 and 2 years after treatment discontinuation.
Results
There was a significant increase in LBMD *z*-score from baseline to before treatment discontinuation in both groups (from −2.7 ± 1.8 to 0.3 1.6 in PAM; from −2.6 ± 2.3 to 1.6 ± 1.7 in ZOL). LBMD *z*-scores were maintained at 1 and 2 years after treatment discontinuation in both groups (0.8 ± 1.8 and 1.0 ± 1.4 in PAM; 0.9 ± 2.6 and 1.7 ± 1.8 in ZOL). While there was no significant difference in LBMD *z*-scores over time between two groups, the total number of infusions was significantly higher in PAM group than ZOL group (12.5 ± 7.8 vs 6.1 ± 2.5 infusions, $P = 0.02$). Fracture rates decreased significantly during treatment in both groups (from baseline of 2.2 ± 4.2 per year to 0.6 ± 0.8 per year in PAM; from 1.9 ± 2.9 per year to 0.3 ± 0.5 per year in ZOL). After treatment discontinuation, fracture rates remained low in both groups (1.9 ± 4.2 in PAM, 0.5 ± 0.7 in ZOL).
Conclusions
PAM and ZOL were both effective therapy for children with OI, with sustained BMD improvement for 2 years after treatment discontinuation. However, fewer infusions were required in ZOL than PAM to achieve similar effects. These results suggest that ZOL had superior potency and efficacy to PAM. Further study is needed to evaluate long-term safety and efficacy of ZOL in patients with OI.
Disclosure
The authors declared no competing interests.
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P40

Painful hip in 19-months old represents an intertrochanteric fracture following a low energy injury

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Hip fractures in children are extremely rare and account for less than 1% of all fractures in children. Most orthopaedic surgeons will treat only a few such fractures in a lifetime. They are associated with high complication rate because the vascular and osseous anatomy of the child's proximal femur is vulnerable to injury. Knowledge of the blood supply to the immature proximal femoral epiphysis is necessary to adequately manage these injuries. Hip pain in children is a diagnostic challenge for every physician due to the variety of possible causes from mild transient to potentially life threatening conditions.
19 months old boy was brought to the hospital by his parents after sustaining a fall at home. He was unable to weight bear on his left leg. Detailed history revealed that the boy has fallen whilst playing from his standard size bed and there were no underlying medical conditions.
Clinically the patient was afebrile, oriented with no obvious deformity swelling or bruising in his left leg. Passive movements of left hip were painful. Plain radiographs of left hip demonstrated some radiolucency around lesser trochanter on AP and in the metaphyseal region on LAT views. Blood tests were normal and the diagnosis of undisplaced intertrochateric fracture was made. Patient was treated with rest, pain control and no cast immobilisation. Weekly radiographs to monitor the fracture position revealed callus formation around the fracture site at 6 weeks.
The patient made full recovery and no complications were encountered during the next 2 years.
The majority but not all of the hip fractures in children are caused by severe, high-energy trauma. Not all fractures can be detected on plain radiographs early. Undisplaced fractures may appear as faint radiolucencies. Special studies may be required to reveal an occult fracture. In a patient with posttraumatic hip pain without evidence of a fracture, other diagnoses must be considered including synovitis, haemarthrosis, infection, child abuse, stress fracture. Patients should be followed with plain radiographs for at least 2 years after fracture to rule out late onset of AVN.
Disclosure
The authors declared no competing interests.
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P41

Percutaneously performed image-guided radiofrequency ablation for the treatment of a unifocal eosinophilic granuloma of the femur in a 16-year-old boy

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Background
Eosinophilic granuloma (EG) typically affects children in the first two decades of life, mainly involving vertebrae and long bones. This study presents the first –to the best of our knowledge - case of a unifocal EG of the femur, successfully treated with percutaneous image-guided radiofrequency ablation (RFA), which was monitored pre- and post-ablation with MRI-scans to validate the efficacy of this method.
Presenting problem
A 16-year-old boy was referred reporting gradually increasing pain in his right femur with an onset of approximately 2 months. Plain radiographs, CT- and MRI-scans, revealed a large lytic lesion in the femoral diaphysis with periosteal reaction without extension to the adjacent soft tissues. C-arm guided core needle biopsy performed with an 8 mm trocard under general anesthesia set the diagnosis of EG. Further imaging (radiographs and Tc99 bone scan) confirmed its unifocal type.
Clinical management
RFA took place in the CT suite room under general anesthesia. A thin biopsy needle was initially introduced through the thickened femoral cortex *via* the biopsy track. A 10 cm, 11 gauge plain electrode access system (RITA medical system) was used. The RFA procedure initiated following confirmation that the tip of the plain electrode was placed at the center of the lesion. The tip was heated up to 90–94 °C for 8 min. After a cooling period, the electrode, the probe and the canula were safely retracted. The patient reported immediate pain relief and was discharged the day after. He was advised to walk without bearing weight with the use of two crutches for one month. He underwent MRI-scans at 3, 6, 12, 18, 24 and 36 months after the RFA, confirming the complete necrosis of the EG and the subsequent focal regenerative procedure. He is currently symptoms-free, able to full-weight bearing and actively participating in athletic activities.
Discussion
Three more patients (English literature) suffering from EG were successfully treated with RFA. Our study confirmed the efficacy of the method by imaging studies as well. RFA seems to be a safe, simple and efficient method for the treatment of unifocal EG, providing fast relief from symptoms and significantly decreased morbidity.
Disclosure
The authors declared no competing interests.
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P42

Levels of vitamin D according to severity of motor function disorder and the level of bone mineral density in children with cerebral palsy

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Objective
To establish the difference between deficiency, insufficiency and normal results of vitamin D according to severity of motor function disorder and the level of bone mineral density in children with cerebral palsy.
Methods
Investigation encompassed 23 children, both genders, between 6 and 17 years of age, with diagnosed cerebral palsy, who were hospitalized between January 1 and December 31, 2014. Bone mineral density (BMD) was established using Dual-energy X-ray Absorptiometry – DXA method, at L1–L4 lumbar vertebrae and at the femur neck, and BMD results were analyzed according to criteria by ISCD Pediatric Position Statement from 2008. Severity of motor function disorder was assessed using Gross Motor Function Classification Scale (GMFCS). Vitamin D status was also analyzed. Normal values were defined as levels of 25(OH) D above 75 nmol/l. Deficiency of vitamin D was determined by values below 25 nmol/l and results between these two values as vitamin D insufficiency. A difference was analyzed between patients with insufficient, deficient and normal levels of vitamin D in correlation to BMD and GMFSC. In statistical analysis, descriptive statistics and Chi-square test were used.
Results
From total number of subjects, 56.5% were boys and 43.5% girls, with average age of 13 ± 3.565 years, whose z-score of spine was -2.00 ± 1.73, and z-score at the hip was -2.00 ± 1.33. In half of patients levels of vitamin D were determined, and from those 58.3% were deficient, 41.7% insufficient, and no subjects had normal levels of vitamin D. Regarding GMFCS, there is no statistically significant difference between patients with vitamin D deficiency and insufficiency ($\chi^2 = 3.36$, df = 1, $P = 0.067$) although 100% of patients with vitamin D deficiency has Category V at GMFCS, while 40% patients with vitamin D insufficiency has Category IV at GMFCS, a 60% has Category V at GMFCS. Regarding BMD, there is no statistically significant difference ($\chi^2 = 0.900$, df = 1, $P = 0.343$) between patients with vitamin D deficiency and insufficiency, although all deficient patients also have osteoporosis.
Conclusion
Patients with lower level of vitamin D also have lower level of BMD and more severe cerebral palsy, pointing to the need for adequate supplementation of this vitamin.
Disclosure
The authors declared no competing interests.

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P43

Efect of nutritional status on bone density in children with cerebral palsy

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Objective
The aim of the study was to establish effect of nutritional status on bone mineral density in children with cerebral palsy.
Methods
The nutritional status was established in 23 children, both genders, with cerebral palsy, who were hospitalized at the Clinic for children habilitation and rehabilitation and at the, 'Veternik' Home, between January 1 and December 31, 2014. Evaluation of nutritional status has been done based on BMI. BMI percentiles were expressed according to gender and the chronological age, based on WHO norms and recommendations from 2007. Assessment of bone mineral density was done using osteodensitometry (dual X-ray absorptiometry-DXA). In statistical analysis, descriptive and nonparametric statistics were used.
Results
From total number of subjects, who were between 6 and 17 years of age, even 20 (87%) was malnourished, and only three subjects were fed using percutaneous endoscopic gastrostomy (PEG). Assessment of bone mineral density has been done, where z-score at the spine was -2.00 ± 1.73, and z-score at the hip was -2.00 ± 1.33. By Spearman's correlation coefficient it was established that there is a statistically significant connection between BMD at the spine and BMI (ρ 0.737). This correlation is positive, with statistical significance at the level of 0.01. There is a statistically significant connection between z-score at the spine and BMI, with statistical significance at the level of 0.01. BMI categories of malnourished and non-malnourished subjects were compared to the z-score, using chi-square test (χ^2) and no statistically significant difference was found.
Conclusion
Nutritional status in children with cerebral palsy, assessed using BMI, points that lower nutritional status is connected to lower bone mineral density.
Disclosure
The authors declared no competing interests.

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P44

Closed image-guided vs open biopsies in children with bone lesions: a retrospective review of 112 biopsies performed on 104 patients

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Introduction
Biopsy is a milestone in the diagnosis and treatment of skeletal lesions. Closed core-needle biopsy under computed tomography (CT) guidance is the gold standard. Open biopsy on the other hand may lead to more secure diagnosis.
Objectives
Aim of this retrospective case-series study was the review of all biopsies (closed and open) performed at our department during the last eleven years in children suffering from bone tumours and the evaluation of the diagnostic accuracy of the closed procedure.
Methods
We retrospectively reviewed the case notes of all children with bone lesions who were hospitalized at our department and underwent biopsies (closed or open). The necessity for additional open biopsy, the validation of the closed biopsy's result with that of the definite pathology report following the excision of a lesion (when excision was performed) and the complication and morbidity rates accompanying closed and open biopsies were registered and analyzed.
Results
Between December 2003 and December 2014, a total of 112 biopsies were performed on 104 children (54 girls and 50 boys) suffering from 24 benign and 80 malignant skeletal lesions. A closed biopsy under CT-scan image guidance was initially performed under anesthesia in all cases. In 13 cases (7.7%) an open biopsy was additionally required. In 87 patients, the lesion was excised. The final pathology report of the excised specimen was in accordance with the initial report which was based on the biopsy tissue in 83 cases; in the remaining 4 cases there was a discrepancy between the two reports. In 3 out of these cases a closed biopsy had been performed. No complications developed following closed biopsies. Two patients had mild postoperative hematomas after open biopsies. An extraosseous migration of a primary aneurysmal bone cyst following closed CT-guided biopsy also developed, which required surgical intervention.
Conclusion
Closed image-guided core needle biopsy seems to be the gold standard method to accurately and efficiently obtain tissue for pathologic examination for benign and malignant skeletal lesions. When performed by experienced radiologists, this method is accompanied by very high success rates, less morbidity than the open and very high rates of diagnostic accuracy.
Disclosure
The authors declared no competing interests.

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P45

Skeletal dysplasia with short stature and a Larsen-like phenotype due to a homozygous mutation in B3GAT3

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Proteoglycans are abundant and structurally complex bio macromolecules. They reside on the cell surface and are a major component of the extracellular matrix including bone. Defective formation of proteoglycans may case pleiotropic connective tissue syndromes including EDS-like and Larsen syndrome–like phenotypes.

We report on a girl with disproportionate short stature and joint laxity with pes planus and radial head dislocation. She was previously assigned to Spondyloepimetaphyseal dysplasia with joint laxity type 1 (SEMDJL1) which is characterized by vertebral abnormalities and ligamentous laxity that result in spinal misalignment and progressive severe kyphoscoliosis, thoracic asymmetry, and respiratory compromise resulting in early death. The phenotype was similar, but except atlantoaxial hypermobility she did not develop scoliosis. This prompted us to Whole-Exom-Sequencing for a recessive mutation in a consanguineous mating. Nonaxial skeletal involvement included elbow deformities with radial head dislocation, genu valgum, flat feet, and tapered fingers with spatulate distal phalanges. The girl had a round face, flat midface, prominent eyes with blue sclerae, and a long philtrum. Decreased bone density was reported in most of the patients

Final height was 130 cm (-5.3 SDS),weight 37 kg ($<3^{rd}$ centile), normal cognitive function.

Whole Exome Sequencing by SOLID 5500 (ThermoFIsher) revealed a homozygous missense mutation in B3GAT3-gene coding for Glucoronyltransferase I (enzymatic step in the Golgi apparatus for a linkage region synthesis of proteoglycans i.e heparan sulfate): c.416C>T, p.Thr139Met. This residue is highly conserved and predicted as pathogenic by Polyphen-2 and MutationTaster.

We add an additional patient to a group of patients with short stature and joint laxity caused by mutations in the linker region of glycosaminoglycans (GAG) including syndromes with mutation in B3GAT3, B3GALT6 (Ehlers-Danlos-like), B4GALT6 (Ehlers-Danlos-like syndrome with kyphoskoliosis), B4GALT7 (Larsen of Reunion Island Syndrome).

Disclosure

The authors declared no competing interests.

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P46

Evaluation of the use of a dynamic elastomeric fabric orthosis to improve truncal stability in a young child with osteogenesis imperfecta

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Osteogenesis imperfecta (OI) is most commonly caused by a defect in the gene that produces type I collagen. Features include fractures and ligamentous laxity. Reduced muscle tone is often seen, which can result in gross motor delay in younger children.

Dynamic elastomeric fabric orthoses (DEFOs or lycra garments) are widely used in children with low truncal muscle tone, have been shown to improve posture, and increase stability. There is no research in the use of DEFOs in children with OI and there has been minimal clinical use in the UK.

We assessed the use of a DEFO for tolerability and functional outcome in a child with OI and low truncal tone.

An 11-month-old girl with OI was referred to the physiotherapy department for gross motor delay and poor posture. She was being treated for vertebral compression fractures but concerns were raised that her sitting posture might exacerbate her spinal deformities. On assessment she was excessively kyphotic with decreased truncal tone. She was able to sit independently with frequent stabilisation using her arms.

A bespoke DEFO was manufactured to a specification which allowed safe application, minimising handling and risk of fracture. The DEFO was worn for 9 hours a day for 6 months. Video assessments with and without the DEFO were obtained and sitting stability was quantified as the length of time both hands were used for play rather than for balance.

After 1 month of use, the DEFO increased hands-free sitting time from a maximum of 2–7 seconds. This enabled the child more engagement with her fine motor activities. Parents reported that during the 6 months, the DEFO was well tolerated and her confidence and activity was increased whilst wearing it.

This case demonstrates that bespoke DEFOs can be tolerated and may be useful in the management of children with reduced tone and delayed motor skills in OI. More work is needed to evaluate poor truncal tone in children with OI and enable promising therapeutic interventions to be objectively assessed.

Disclosure

The authors declared no competing interests.

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P47

Ethnic and gender differences in metacarpal dimensions in black and white South African children from pre-puberty through adolescence

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Bone accrual and the attainment of peak bone mass influence an individual's predisposition to fracture or osteoporosis later in life. The developmental tempo and the movement of the periosteal and endosteal surfaces of the appendicular skeleton during growth result in variations in bone mineral content and density. During puberty the differential in peak height and peak bone mass accretion negatively influence bone strength. A surrogate measure of bone strength is the metacarpal index (MI) which has been shown to predict fracture risk in adults. This longitudinal study describes the differences in the metacarpal bones from pre-puberty through adolescence by ethnicity and gender. 689 subjects from the South African (SA) Birth to 20 Cohort were studied annually between 9 and 22 years of age. Radiogrammetry was performed on 4590 hand-wrist x-rays of black and white boys and girls. Total bone length (L), and cortical and medullary width were measured at the midshaft of the second metacarpal using digital vernier callipers calibrated to two decimal places. The MI was derived by dividing the combined cortical thickness by total bone width (W). Cross-sectional statistical analysis (t-test) showed no ethnic differences in L and W at all ages. Compared to boys, black and white girls had significantly lower L from 14–20 years and narrower W at all ages ($P<0.05$). Data were not adjusted for height. In both black boys and girls the MI was lower than in their white peers indicative of lower cortical thickness relative to bone width in black children ($P<0.05$). Comparison of the MI by gender showed that at all ages black girls had a greater MI than boys, however, in white children a significant gender difference was only present between the ages of 10 and 14 years ($P<0.05$). The lower MI in black boys and girls conflicts with the lower prevalence of fracture rates reported in black SA adults and children compared to their white counterparts. Differences in metacarpal dimensions are suggestive of ethnic and gender disparities in bone mass accrual in SA children from pre-puberty through adolescence.

Disclosure

The authors declared no competing interests.

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P48

Bone mineral density, vertebral compression fractures and pubertal delay in patients with autosomal recessive epidermolysis bullosa

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Severe generalised recessive dystrophic epidermolysis bullosa (RDEB) is a rare disorder resulting from loss of function mutations in the type VII collagen gene (*COL7A1).* Although RDEB is characterised by severe skin blistering and erosions following minor mechanical trauma, it is a multisystem disorder with pubertal delay and low bone mass as part of the many complications.

Children with RDEB have been described as having inadequate gains in bone density, so we hypothesised that pubertal delay may be a contributing factor. We sought to describe the prevalence of pubertal delay, low bone mass, vertebral compression fractures (VF) and scoliosis in children with RDEB aged 15-18y and compare this to the bone health of pre-pubertal RDEB children.

This was a retrospective, observational study of 40 patients with RDEB aged 7–8 and 15–18 years ($n=20$ in each group). Primary outcome measures were lumbar spine areal bone mineral density (aBMD), age adjusted z-score, VF, scoliosis and pubertal delay.

The aBMD (mean ± s.d.) of children aged 7.8 ± 0.5 years was 0.54 ± 0.1 g/cm^2 with z-score of −1.8 ± 1.1. 36% had VF and 11% had scoliosis.
This compared with aBMD of children aged 16.1 ± 0.8 years of 0.72 ± 0.2 g/cm^2 with z-score of −3.9 ± 1.5. 40% had VF and 30% had scoliosis. 84% of these children had pubertal delay.
Despite an increase in aBMD ($P < 0.001$) with age, there was a highly significant decrease in BMD z-score ($P < 0.0001$). Surprisingly patients with VF did not have significantly different BMD z-scores from those without VF (P = ns, t-test).
Pre-pubertal children with RDEB have VF and low BMD z-scores that deteriorates with age. By the ages of 15–17, 84% of children have pubertal delay, which is likely to compound pre-existing poor bone health.
Despite early preventative interventions such as optimising nutrition, vitamin D supplementation and physiotherapy, complications including vertebral compressions and scoliosis are present from an early age and worsen over time. Early medical preventative interventions, such as bisphosphonate therapy should be considered in patients with RDEB.
Disclosure:
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P49

Using high-resolution peripheral quantitative computed tomography (HRpQCT) to better understand the skeletal response to exercise
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To use HRpQCT to investigate the effects of short term but intense exercise on the bone architecture of the distal radius in exercise-naïve women, with the ultimate aim of developing exercise regimes for children that will maximise their peak bone mass.
We have recruited 16 of 20 proposed exercise-naïve women, aged 18–25, for a 12-week exercise study. The exercise consists of supervised hammering of a metal plate, using their dominant arm, 3 days a week for 12 weeks. Each session consists of 40 hammer blows separated by a 10 second rest between each blow. Baseline HRpQCT of both wrists will be compared to scans obtained after the last exercise session (April 2015).
The mean baseline age of participants was 21.4 (±1.165 s.d.) years. The mean baseline BMI was 22.1 (±2.584 s.d.) kg/m^2. A paired t-test of baseline average bone density, trabecular bone density, compact bone density, trabeculae number, trabecular thickness and cortical thickness showed no significant difference between the right and left radii at baseline ($P > 0.05$). Differences between baseline and post-exercise HRpQCT values will be tested for significance using a dependent t-test. Assessment of least significant change will indicate whether the changes are real or due to inherent variability.
The study will show what effect a relatively short but intense exercise regimen has on bone microarchitecture in exercise-naïve women and will indicate the feasibility of such a study in children and young people.
Disclosure
The authors declared no competing interests.
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P50

'Double trouble': Duchenne muscular dystrophy and osteogenesis imperfecta in one patient – a case report
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Background
Duchenne muscular dystrophy (DMD) is characterised by progressive muscle weakness leading to loss of mobility, cardiomyopathy, and respiratory insufficiency. Typical initial manifestation in boys (X-linked disorder) comprises proximal muscle weakness and calf hypertrophy. Osteogenesis imperfecta (OI) is a clinically heterogenous heritable connective tissue disorder with increased bone fragility. Fractures rise from little or no apparent trauma.
Presenting problem
We put forward a five-years-old patient with 'double trouble': ***DMD*** and OI. He is a child of unrelated parents. His paternal family history was positive for OI, including the patient's father, grandmother and great-grandfather.
Clinical management
Our patient was presented at 11 months of age due to high liver blood tests following gastroenteritis. Investigation revealed elevated creatinkinase. Hypotonia, diminished deep tendon reflexes, and calf hypertrophy arose about the possibility of muscular dystrophy. DNA analysis confirmed deletion of exons 48–52 in the dystrophin gene consistent with diagnosis of DMD.
At 2 years of age, humeral fracture appeared with unknown mechanism and 1 month later he sustained tibial fracture due to inappropriate trauma mechanism. Targeted genetic testing identified causative mutation c.2667+5G>A in the patient's COL1A1 gene. This is a type of splice site mutation due to missing donor splicing site, which has not been described yet. However, similar mutation types were described in other introns of the gene. Lumbar spine bone densitometry revealed excessively low bone mineral density (z-score −3.95, adjusted for height age). 2 years of treatment with intravenous pamidronate and 1-α-hydroxy vitamin D resulted in significant improvement (adjusted z-score −0.93). Height gain is 16 cm and weight gain 3.4 kg within 27 months. He is able to walk 300 m without rest. Hypotonia persists as well as low tendon reflexes, calf pseudohypertrophy, and positive Gower's sign. No further fracture appeared.
Discussion
As dystrophin gene mutations may be carried through an unaffected mother (or as '*de novo*' mutation), the family history of DMD is frequently negative. Mutations in COL1A1 are mostly inherited through an autosomal dominant pattern with positive family history of OI.
Muscle weakness, mobility limitations and developmental motor delays could be shared by both diseases resulting in diagnostic difficulties.
Disclosure
The authors declared no competing interests.
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P51

Abstract withdrawn

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Association of dietary calcium intake and body fat with hypertension in Indian adolescents
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Objective
Low dietary calcium intakes and increasing adiposity in Indian adolescents may increase their risk of hypertension (Sanwalka *et al.*, *Asia Pac J Clin Nutr.* 2010, Khadilkar *et al.*, *Int J Pediatr Obes.* 2010). Therefore, the aim of the present study was to explore association of dietary calcium intakes and body composition with blood pressure in 10–14 year old Indian adolescents.
Method
370 apparently healthy adolescents (190 boys) with mean age 12.1 ± 1.3 years were studied from five major Indian cities. Anthropometry (height, weight, BMI, waist circumference), blood pressure (BP-mercury sphygmomanometer), BIA–(Body composition analyser-Tanita-SC-240, %fat, muscle mass) and 24 h-Diet recall (C-diet, V2.0) were recorded using standard protocols (data addition ongoing).

Results
Subjects were divided into sub groups as with normal BP, pre-hypertension and hypertension using height & gender matched Indian reference data (Raj *et al.*, *Indian Paediatrics*, 2010). Hypertension was found in 6% boys and 4% girls. Subjects with pre-hypertension and hypertension had significantly higher weight and BMI *z*-scores, waist & fat % ($P<0.05$). Dietary calcium intakes were significantly lower in the group with hypertension ($P<0.05$). Majority of the subjects (80%) from higher BP groups had daily calcium intakes below RDA than normal BP subjects (58%). Other nutrient intakes were similar among all the three groups ($P>0.1$). Dietary calcium intake was negatively correlated with BP (systolic and diastolic) ($r=-0.240$, $P<0.0001$) even after adjusting for energy intake. Further, BP was also positively correlated with BMI ($r=0.54$), waist ($r=0.52$) and body fat% ($r=0.56$) ($P<0.001$). Generalised linear model analysis revealed that dietary calcium, body fat % and waist were significantly associated with blood pressure ($P<0.01$) even after adjustment for height.
Conclusion
Low dietary calcium intakes and high adiposity increase the risk of hypertension in Indian adolescents.
Disclosure
The authors declared no competing interests.
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P53

Somatic COL1A1 mosaicism in a newborn with osteogenesis imperfecta
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Background
Osteogenesis imperfecta (OI) is a hereditary connective tissue disorder characterized by increased bone fragility and low bone mass. The different types of OI may be distinguished by their clinical features and the causative genes, with *COL1A1* and *COL1A2* genes as the most frequent. The guidelines for OI genetic diagnosis first recommends the screening of *COL1A1* and *COL1A2* genes using Sanger sequencing. However, this method has limitations to detect somatic mutations with low allele frequency, which could be overcome with the use of next generation sequencing (NGS) technologies.
Presenting problem
We describe an infant born from a bichorionic twin gestation at 33 weeks. At 8 days of life, she presented displaced right femur fracture. The skeletal series also revealed ribs fractures and thoracic vertebral compression. Bone metabolism screening was normal. Despite no familial history of OI was registered and no other features of OI were detected, a genetic study was performed.
Clinical management
COL1A1 and *COL1A2* genes were screened using Sanger sequencing. The analysis of *COL1A1* detected the c.1129G>A transition, which generates the already known p.Gly377Ser mutation. However, analyses of chromatograms revealed a marked disbalanced fluorescence intensities among wild-type and mutated alleles, suggesting a potential somatic *COL1A1* mosaicism. To address this issue, we performed targeted deep sequencing using genomic DNA extracted from blood and mucosal swabs. This analysis revealed the c.1129G>A mutation in both samples at a similar allele frequency (25%). The mutation was not detected in patient's parents, supporting its *de novo* nature. The patient started treatment with pamidronate, calcium and vitamin D, and no fractures occurred during 20 months of follow-up.
Discussion
We describe the first case of somatic *COL1A1* mosaicism causing OI. Due to the relatively high frequency of the mutated allele, Sanger sequencing was able to detect it and NGS technologies finally confirmed and quantified the degree of mosaicism. This approach enabled us to definitively diagnose this patient, and support NGS as the recommended technology to evaluate gene mosaicism.
Disclosure
The authors declared no competing interests.
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P54

Vitamin D overdose: Poor dosage guidelines for babies?
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Background
A 9-month-old boy was diagnosed with rickets at the age of 6 months. He was born at term in India, following a normal pregnancy. Mother had taken folic acid and calcium, but not vitamin D, as this is the policy for pregnancy vitamins in Kerala.
Presenting problems
At 6 months of age he was seen for routine vaccination. The paediatrician noted a prominent forehead and swollen wrists. Wrist x-ray was said to show early rickets. Blood tests showed 25(OH) vitamin D < 7.5 nmol/l. The baby was treated with Colecalciferol 60 000 units/once a week for 6 weeks.
Repeat blood test 6 weeks later in India showed 25(OH) vitamin D > 175 nmol/l. The calcium and phosphate levels were normal and Alkaline Phosphatase was 339 IU/l. The paediatrician changed the prescription to calcium and vitamin D syrup (Ca 250 mg/Vit D 125 units in 5 ml) 5 ml per day.
Clinical management
The baby was reviewed at 8 months of age by a GP in the UK. Serum vitamin D level was in the overdose range at 576 nmol/l, with normal levels of calcium and phosphate and alkaline phosphatase (262 IU/l). He was then seen in a paediatric metabolic bone clinic where no clinical, biochemical or radiological signs of rickets were seen. The original radiograph from India was reviewed and was normal. PTH and urine calcium were measured and were normal with no signs of toxicity. However the $1.25(OH)_2$ vitamin D was high at >380 pmol/l.
Discussion
The dosage given in India (total vitamin D dose 360 000 units) is well within the current British dosage recommendations. These are that children aged 6 months–12 years be given 6000 units daily for 8–12 weeks (total dose of 504 000 units). This suggests that for small babies the current dose recommendations need revision.
Disclosure:
The authors declared no competing interests.
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P55

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P56

Abnormal functional responses of osteoblasts to leptin in adolescent idiopathic scoliosis
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Objectives
Adolescent idiopathic scoliosis (AIS) is a complex three-dimensional structural deformity of the spine and its etiology remains unknown. Girls with AIS have taller stature, longer arm span, lower BMI, and generalized osteopenia. Leptin has

been postulated as one of the etiologic factors of AIS because of its important physiological functions in neuro-osseous development affecting skeletal growth, bone metabolism, energy expenditure and body composition. Previous studies on the relationship between leptin and HR-pQCT derived bone quality parameters had found abnormal correlations in AIS girls, and suggested possible abnormalities in the leptin regulated bone metabolic pathways. This study aimed to investigate and compare the effect of leptin on the functional responses of osteoblasts in AIS and control subjects.

Methods

In vitro assays were performed on osteoblasts cultured from biopsies obtained intraoperatively from 12 AIS girls and six control subjects. The osteoblasts were exposed to different concentrations of leptin (0, 10, 100, 1000 ng/ml). Cell proliferation was evaluated with MTT assay; differentiation with ALP activity assay and osteocalcin ELISA; and mineralization with von Kossa staining.

Results

Leptin stimulated control osteoblasts to proliferate in a dose dependent manner, while AIS osteoblasts showed no proliferative response to leptin. For differentiation, control group showed significant increasing trends in ALP activity and osteocalcin secretion to increasing leptin concentrations, while no responses were observed in the AIS osteoblasts (Fig. 1A). For mineralization, control osteoblasts showed increasing amount of calcium nodules to leptin concentrations, and again no response was observed in AIS (Fig. 1B).

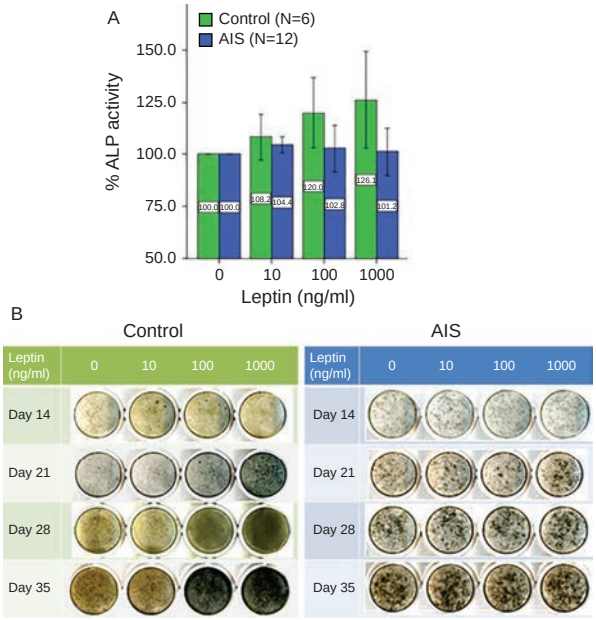

Figure 1A. Effect of leptin on alkaline phosphatase (ALP) activity of osteoblasts from control and AIS patients after 14 days of leptin treatment. B. von Kossa staining of control and AIS osteoblasts at day 14, 21, 28, and 35. Formation of calcium nodules in control osteoblast increased as the days of treatment and leptin concentration increases, but AIS osteoblast showed no response to leptin treatment.

Conclusion

The results indicated that the AIS osteoblasts had significantly lower functional response to leptin challenge when compared with controls. The observation might be related to dysfunction of the leptin signaling pathway and accounting for the low bone mass and deranged bone quality reported in AIS. Further studies would be warranted.

Disclosure

The authors declared no competing interests.

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P57

Fractures in infants – a population-based study over 15 years in Helsinki, Finland

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Objectives

Fractures are common in older children. There are only few population-based studies on fractures in infants. Child abuse is a possible trauma mechanism, especially in younger children. New national guidelines for increasing awareness of child abuse and screening for suspected non-accidental traumas in Finland were given in 2003. Our goal was to establish fracture incidence and epidemiologic fracture patterns in children under the age of 1 year.

Methods

We carried out a retrospective population-based study in Helsinki, Finland. Our data consists of patients who had a fracture before the age of one year during years 1998–2012, only birth traumas were excluded. Details regarding patient demographics, fracture site, and trauma mechanism were collected. Fracture diagnosis was always confirmed radiographically.

Results

In total, 338 children (54% males) with a fracture were diagnosed during the study period in Helsinki. Of these, 209 (62%) were younger than 9 months at the time of the diagnosis. The overall annual incidence of fractures in infants was 36.4/10 000 (median, range 18.1–55.6), it was highest in 2004. During the research period, annual fracture incidence decreased by 29%, the median incidence being 44.0/10 000 per year in 1998–2006 and 25.4/10 000 per year in 2007–2012 ($P=0.026$).

In children aged 0–8 months, skull fractures were most common (59%) followed by clavicle (14%), and femur (12%) fractures. In children aged 9–12 months skull fractures represented 40% of cases followed by fractures in crus (21%) and antebrachium (18%).

Conclusion

The anatomic distribution of fractures is age-dependent in infants. A significant decrease in the overall annual incidence of fractures in children under 1 year of age was seen during the study period. The role of non-accidental trauma as fracture mechanism, more detailed trends, and other contributing factors remain to be elucidated in further analysis of the data.

Grants

Päivikki and Sakari Sohlberg Foundation, Foundation for Pediatric Research, Sigrid Juselius Foundation, all Helsinki, Finland.

Disclosure

The authors declared no competing interests.

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P58

Music therapy as an avenue to promote healthy eating, exercise and bone health in children

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Objectives

The obesity in children and adolescents is in an exponential rise, particularly in the United States. New research indicates that high adiposity could be detrimental for both bone and muscle, *via* fat infiltration in those tissues, leading to the osteosarcopenic obesity[1]. Therefore, healthy weight in children is crucial for bones and muscles. Our objective was to develop a music therapy program to improve children's dietary and exercise habits and by that promote healthy weight and bones.

Methods

We report the results of three pilot studies conducted in children ages 6–9 years, where the original music intervention, including custom composed music and educational lyrics with drumming and singing were combined with jumping, running and calisthenics. The studies included 78 children, mostly African Americans, mostly overweight or obese and each intervention lasted 6 weeks, three times/week, 45 min/session. Anthropometrics were measured and behavioral attitudes and knowledge about healthy life styles were assessed.

Results

The first study ($n=7$) resulted in slight decrease in BMI and improved attitudes about exercise and healthy eating. Second study ($n=42$) showed gains in knowledge and attitude about food and exercise, but anthropometries were inconclusive, due to low ratio of researchers to children and probably unreliable measurements. The third study ($n=29$) resulted in decreased BMI and waist

circumference by ~5% and 0.9 cm respectively. The results for children's nutritional knowledge showed increase of 0.16 points for eating habits and 0.83 points for information on food taught during intervention. The children's attitude toward school increased and they consistently expressed positive views about music intervention. Finally, the behavior analysis indicated a decrease in off-task behavior of 2.1% during the intervention.

Conclusions

To our knowledge, this is the first study to use structured and active music-making in children for their diet and exercise improvement. The music activities showed to be useful and motivational and promoted positive behavior, team spirit and increased on-task behavior. For the authors, a special symbolism presents the possibility of presenting this study in Salzburg, a birthplace of one of the greatest composers of all times. Supported in part by Tanita grant

Reference

Ilich JZ, Kelly OJ, Inglis JE, Panton LP, Duque G, Ormsbee MJ. Interrelationship among muscle, fat, and bone: Connecting the dots on cellular, hormonal, and whole body levels. Ageing Res Rev 2014 15 51–60.

Disclosure

The authors declared no competing interests.

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P59

Vibration treatment can enhance the bioactive response of osteoblasts to vitamin D in adolescent idiopathic scoliosis patients

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Objectives

Adolescent idiopathic scoliosis (AIS) is a complex three-dimensional spinal deformity associated with low bone mass. Our previous clinical trial demonstrated the anabolic bone effect of vibration treatment (VT) at the femoral neck in AIS subjects. The therapeutic effect was more pronounced in those with optimal serum 25(OH) Vit-D level (>40 nmol/l). To investigate possible factor interaction between Vit-D and VT on their anabolic bone effects, this *in-vitro* study was performed to evaluate whether VT could positively modulate the response of AIS primary osteoblasts to Vit-D.

Method

Osteoblasts were isolated from iliac crest biopsy harvested from AIS subjects ($n=7$) and non-AIS controls ($n=3$). Osteoblasts were treated with 0.10 nM and 100 nM of $1.25(OH)_2$Vit-D with or without VT (0.3 g, 35 Hz for 20 min pr day). Cell metabolic activity was determined by Alarma blue. Gene expression of osteogenic markers were determined by real time PCR. Mineralization ability was determined by ALP and Alizarin red staining. Semi-quantitation was done for statistical analysis.

Results

When compared with controls, AIS osteoblasts had lower intrinsic calcium deposition and ALP activity. Enhancement effect of VT on response of osteoblasts to Vit-D as evidenced from increased degree of mineralization, *Runx2, ALP and SPP1* mRNA expression in osteoblasts was more explicitly seen in AIS than in controls.

Conclusion

The greater response of AIS osteoblasts to concurrent treatment with Vit-D and VT might be part of the mechanism underlying the modulating effect of Vit-D level on anabolic bone effects of VT seen in the clinical trial. Further studies looking into the underlying mechanism could shed lights on the etiopathogenesis and other biochemical anomalies that characterize AIS.

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Disclosure

The authors declared no competing interests.

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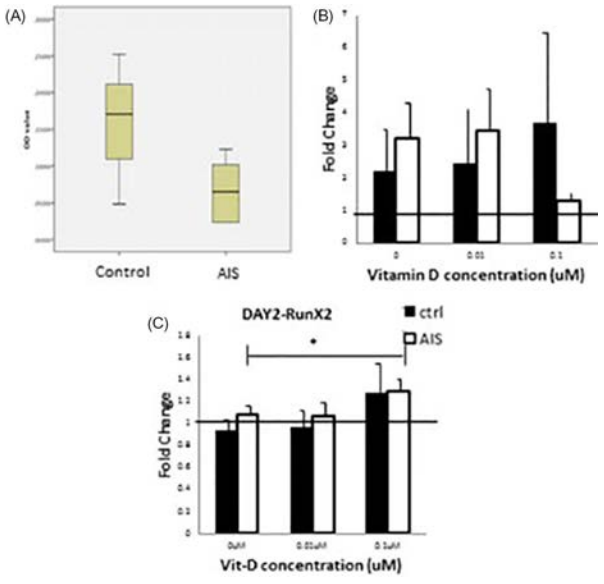

Figure (A) AIS (n=7) formed less calcium nodules than control (n=3) at Day 7 without treatment; (B) OSteoblast of AIS (n=7) showed more mineralization than control with vibration and vitamin D at concentration of 0 uM and 0.01 uM; (c) mRNA expression of RunX2 in AIS was significantly upregulated with vibration and vitamin D at concentration of 0.1 uM ($p<0.05$). Fold change was calculated by vibration relative to non-vibration

P60

Comparing two scanning protocols for high-resolution peripheral quantitative computed tomography for bone quality assessment in young subjects

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Objectives

High resolution peripheral quantitative computed tomography (HR-pQCT) was used to evaluate bone quality and volumetric bone mineral density (vBMD). However, manufacturers only provide a standard protocol for adult but not for growing subjects. The aim of this study was to investigate the difference on measurement between two different HR-pQCT scanning protocols in adolescence with unfused growth plate.

Methods

27 boys and 26 girls aged 13–16 were recruited. Their non-dominant distal radius was scanned by two HR-pQCT scanning protocols consecutively. In Protocol 1, distance between corresponding reference line and first slice of region of interest (ROI) was set at 5 mm, whereas in Protocol 2, that distance between corresponding reference line and first slice of ROI was 4% of the radius length. Paired *t*-test or Wilcoxon signed rank test was preformed to compare the result of measurement.

Results

Total area was lower, cortical area was higher and trabecular area was lower in Protocol 1 as compared to Protocol 2 for both boys and girls. In boys, only trabecular vBMD and trabecular bone volume fraction showed no difference between the two protocols ($P=0.78$ and 0.76). Among all parameters, the difference in cortical thickness between the two protocols was greatest in boys (% diff=20.6%, $P<0.001$). In contrast, only total vBMD and cortical perimeter

showed significant differences between the two protocols in girls (% diff = 3.6% and −1.47%, $P = 0.032$ and 0.05).
Conclusion
Differences in HR-pQCT measurement with Protocol 1 and 2 in both boys and girls stemmed from the difference in location of ROI between the two protocols with the ROI in Protocol 1 being more distal than that in Protocol 2. Greater discrepancy noted between the two protocols in boys was probably due to less overlapping of ROI between the two protocols and that boys have a larger change on bone morphology at the distal radius when compared with girls. Further investigations are warranted to elucidate which protocol gives a more valid evaluation of bone density and bone quality and caution must be exercised when comparing studies that involve different protocols of measurements.
Disclosure
The authors declared no competing interests.
DOI: 10.1530/boneabs.4.P60

P61

Association of vitamin D concentrations with 7-Dehydrocholesterol Reductase in school children in a sun-rich, semi-rural setting in Western Maharashtra, India

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Objectives
Studies have reported prevalence of vitamin D deficiency in Indian children with adequate sunlight exposure (Harinarayan, 2008). The objectives of our study were to A) examine the prevalence of vitamin D deficiency in children with adequate sunlight exposure in a semi-rural setting in Western Maharashtra (18(°N), India and B) explore the association of serum 7-Dehydrocholesterol reductase (7-DHCR) with the serum vitamin D levels.
Methods
This cross-sectional study was carried out in 432 children aged 6–12 years from a public school. Data on demographics, anthropometry (height, weight), body composition (BIA (Tanita, BC-420MA)) was collected by standard methods. Sunlight exposure using validated questionnaire and dietary calcium intake (by 3 day, 24 h recall method; analysed by C-diet, V2.0) were recorded. Fasting serum 25 hydroxyvitamin D (25OHD) (EIA kit by DLD Germany) and 7-DHCR on a sub-sample of 160 (EIA kit by Cusabio) were assessed.
Results
Mean serum 25OHD concentrations were 23.4 ± 4.2 ng/ml; 32% children had serum 25 OHD concentrations ≤20 ng/ml (vitamin D inadequacy) and 68% children had levels ≧21 ng/ml (vitamin D sufficiency) (Institute of Medicine, 2011). All children had a similar sunlight exposure of more than 2 h per day (2.4 ± 0.2 h) and similar dietary calcium density (244.5 ± 85.1 mg/1000 kcal per day). The mean DHCR concentrations were 714 ± 341 pg/ml. DHCR was found to be negatively correlated with the 25 OHD concentrations ($r = -0.2$; $P < 0.05$). A significant negative correlation was also obtained between body fat percentage and serum 25OHD concentrations ($r = -0.2$; $P < 0.01$).
Conclusion
Deficiency of vitamin D was noted in a third of the children despite adequate sunlight exposure. higher DHCR concentrations and body fat percentage were associated with lower concentrations of serum vitamin D. Data collection is still in progress.
Disclosure
The authors declared no competing interests.
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P62

Association of dental and skeletal fluorosis with calcium intake and vitamin D concentrations in adolescents from a region endemic for fluorosis

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Objective
Patan, is a semi urban area in Gujarat, India where fluorosis is endemic (Fluoride concentration in ground water 1.96–10.85 ppm, Patel et al., 2008). Exposure to fluoride is likely to be higher in lower socio-economic class (SEC) due to lack of access to bottled water. Calcium intake and vitamin D status may modify fluorine absorption. Therefore, the aims of this study were to examine: i) prevalence of dental and skeletal fluorosis in children from upper, middle and lower socioeconomic class; ii) association of fluorosis with calcium intake and vitamin D status.
Methods
Cross-sectional study was conducted in 10–14 year apparently healthy adolescents ($n = 90$; boys, $n = 45$), belonging to upper, middle and lower SEC ($n = 30$/SEC, Kuppuswamy scale, 2012) from Patan (Gujrat). Dental fluorosis was graded as mild, moderate, severe by a dentist. Radiographs of right hand and wrist were examined and graded (Teotia *et al.*, 1998). 25OHD and PTH (both using chemiluminescent immunoassay) were measured. Diet was recorded by 24 h recall and calcium intake computed (C-diet 2.1).
Results
Fluorosis was predominantly seen in lower SEC, (Default 1); there were no skeletal deformities. Mean 25OHD concentrations and dietary calcium were 26.3 ± 4.9, 23.4 ± 4.7, 18.6 ± 4 ng/ml and 406 ± 222, 499 ± 192, 690 ± 245 mg/d respectively for lower, middle and upper SEC ($P < 0.05$). PTH did not vary ($P > 0.1$).79% from upper, 50% from middle and none from low SEC had access to bottled water with appropriate fluoride concentrations(http://www.cdc.gov/fluoridation/faqs/bottled_water.htm). There was significant association between fluorosis and SEC (exponential $\beta = 2.5$, $P < 0.01$); 25OHD and calcium showed no significant association.

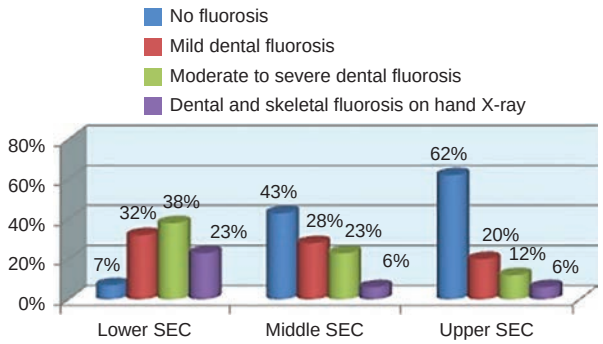

Figure 1 Prevalence (%) of fluorosis in different SEC.

Conclusion
Fluorosis was more common in lower SEC. Relatively adequate calcium intake and 25OHD may have prevented severe skeletal flurosis.
Disclosure
The authors declared no competing interests.
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P63

Dietary calcium intake influences the relationship between serum 25 hydroxyvitamin D concentrations and Parathyroid hormone

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Objectives
Previous studies have reported that the rise in parathyroid hormone (PTH) concentrations may be used to determine the levels of vitamin D adequacy. However, dietary calcium intake may also influence the rise in PTH. In the light of low calcium intakes in Indian adolescents, our aim was to investigate the relative importance of calcium intake in relationship of serum 25 hydroxyvitamin D (25OHD) with intact serum PTH in apparently healthy children.
Methods
A cross-sectional study on apparently healthy adolescents aged 10–14 years ($n=181$), from Gujarat, Western India, was conducted from January 2012 to March 2014. Serum 25OHD concentrations (chemiluminescent microparticle immunoassay), serum PTH (chemiluminescent microparticle immunoassay) were measured. Diet was recorded through 24 h diet recall and calcium intake was computed (C-dietV2). To assess relationship between 25OHD and PTH, data were dichotomized according to median calcium intakes (520 mg) and relationship between serum 25OHD and PTH in the two subgroups were plotted.
Results
Mean levels of 25OHD, PTH and dietary calcium among study population were 17.7 ± 6.8 ng/ml, 37.3 ± 26.1 pg/ml and 570 ± 262 mg /d respectively. Subjects with calcium intakes >520 mg had lower PTH for given vitamin D while those with calcium intake <520 mg had higher PTH values for given vitamin D. 25OHD was negatively correlated with serum PTH at lower as well as higher calcium intake, ($r=-0.606$ and -0.483 respectively, $P<0.01$ for both). The plot (Default 1) revealed existence of curvilinear inverse relationship between 25OHD and PTH; PTH vs 25OHD curve showed a negative shift with increasing calcium intake.

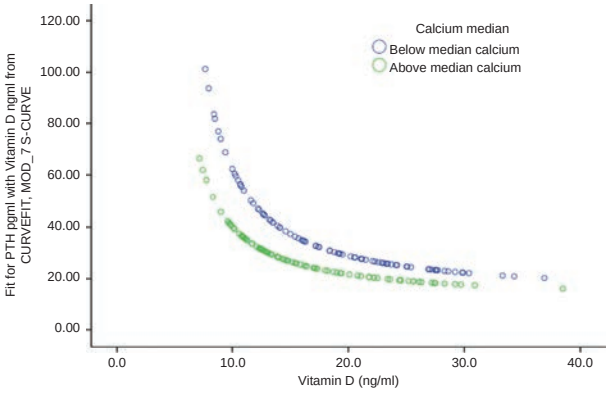

Figure 1 Shift of 25OHD vs PTH curve to left with increasing calcium intake.

Conclusion
Dietary calcium intake influences relationship between 25OHD and PTH. Dietary calcium intake should be taken into account when assessing an individual's serum PTH level.
Disclosure
The authors declared no competing interests.

DOI: 10.1530/boneabs.4.P63

P64

Peripubertal bone quality and density profile of Chinese adolescents in Hong Kong

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Objectives
This study aimed to evaluate detailed bone profiles during puberty for Chinese adolescents in Hong Kong using high-resolution peripheral quantitative computed tomography (HR-pQCT) and dual-energy x-ray absorptiometry (DXA).
Methods
333 healthy girls and 231 healthy boys (12–16-years-old) were recruited from secondary schools. Areal bone mineral density (aBMD) of bilateral femoral necks were measured by DXA while bone quality parameters were measured by HR-pQCT at the non-dominant distal radius. Maturity was assessed by Tanner staging.
Results
While a general increasing trend in bone density across puberty was found in girls, no difference on aBMD and vBMD between Tanner 3 and 4 was noted in boys. aBMD were numerically higher in boys at Tanner 1–3 while the reverse was noted at Tanner 4–5 with the difference reaching statistical significance at Tanner 4 (Default 1). Trabecular vBMD was higher in boys whereas girls had higher cortical and total vBMD especially at Tanner 4–5. Total area, cortical perimeter and trabecular area were higher in boys than girls across all Tanner stages. In contrast, cortical area and thickness were higher in girls especially at Tanner 4–5. Trabecular bone volume fraction and number were higher in boys while trabecular separation was higher in girls at Tanner 3–5.

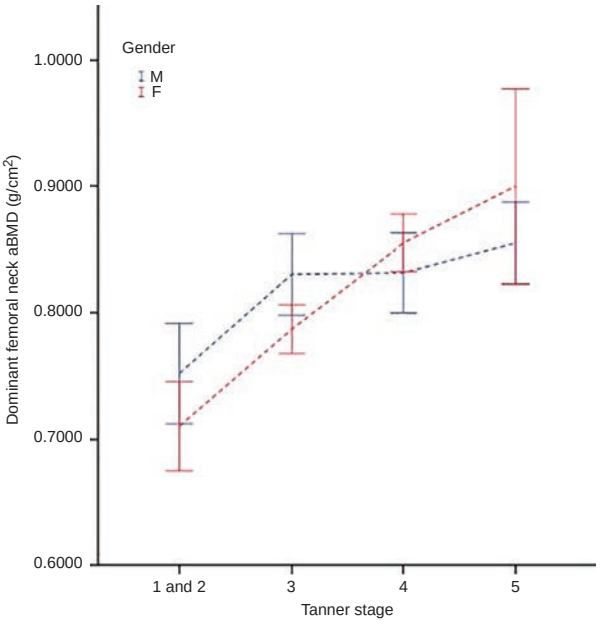

Figure 1 Dominant femoral neck aBMD in chinese boys and girls across puberty

Conclusion
There were differences on bone quality and density profiles across puberty between genders. A general increasing trend in aBMD and vBMD was only found in girls. Gender differences in bone parameters at the cortical and trabecular compartment were notably detected. Whether these were due to discrepancy in linear growth that outpaces mineral accretion in boys and whether estrogenic effect on endosteal apposition was responsible for these findings warrant further studies.
The project was supported by General Research Fund (468411, 468809).
Disclosure
The authors declared no competing interests.

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P65

Results of a specialized rehabilitation approach in osteogenesis imperfecta

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Introduction
Osteogenesis imperfecta is a rare disease leading to immobility by recurrent fractures, immobilization, short stature and muscular weakness. Beside drug treatment and surgical procedures physiotherapy is the most important treatment approaches to increase mobility. The objective of our analysis was to evaluate the effect of a new standardized 12 months physiotherapy concept including whole body vibration over 6 months on motor function and bone mineral density in children with Osteogenesis imperfecta.
Methods
In a retrospective data analysis 53 children (32 male; mean age: 9.1 years, bisphosphonate treatment $n=46$; OI type 1 $n=8$; OI type 3 $n=17$; OI type 4 $n=26$, OI type 5 $n=2$) were analyzed. The 12 months concept included a period of 6 months of whole body vibration and concomitant physiotherapy, resistance training and treadmill training. The concept is structured in two in-patient stays and two periods of three months home-based vibration training. Primary outcome parameter was the gross motor function measure before and after 12 months. iDXA (GE) was used to analyze muscle and bone parameters.
Results
Results of the training period and the follow-up are presented in Table 1:

Table 1

	Change during training	Change during follow up	Change over all
GMFM 66 (score)	3.62	−0.42	3.20
(mean and *P*-value)			
	<0.001	0.60	<0.001
1-min walking (m)	20.25	−3.93	16.3
(mean and *P*-value)			
	0.002	0.733	0.01
BMD L2-L4 (*z*-score)	Not measured do to radiation		0.13
(mean and *P*-value)	reduction		0.43
BMD TBLH (*z*-score)			−0.03
(mean and p-value)			0.66
Height (cm)	2.3	1.8	4.1
(mean and *P*-value)	<0.001	<0.001	<0.001
Height (S.D.)	−0.07	−0.06	−0.13
(mean and *P*-value)	0.445	0.729	0.305
BMI (SD)	0.04	−0.06	−0.02
(mean and *P*-value)	0.893	0.275	0.429

Conclusions
The physiotherapy concept including whole body vibration leads to a significant improvement on gross motor function, lean mass and bone mineral content in children with Osteogenesis imperfecta. Additional the height of the children increased comparable to their age group and they showed no increase of their dwarfism. Therefore this therapeutic approach should be considered as part of an integrated treatment concept in children with OI.
Disclosure
OS and ES are employed by the rehabilitation center.

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P66

Challenges in the management of hip dislocation a patient with Prader Willi syndrome

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Background
Prader Willi syndrome (PWS) is a genetic disorder characterized by severe hypotonia in infancy, hypogonadism, dysmorphic features, early onset obesity and mild mental retardation.
Although hip dysplasia occurs in 10–20% in patients with PWS, hip dislocation requiring surgery is seen rarely. To our knowledge, surgical treatment of hip dislocation in PWS has not been reported before.
We present a case with PWS and hip dislocation and describe the challenges during treatment.
Presenting problem
A two years old boy presented to the Pediatric Orthopedic Clinic with a history of waddling gait. The hypotonia and the micro genitalia led to the diagnosis of PWS at age 1.5 month The genetic test revealed *SNRPN* gene methylation. On physical examination the patient was obese (BMI-S.D. score: +4.5), he had typical facies with frontal narrowing and almond-shaped eyes, small hands, esotrophia and bilateral cryptorchidism with small penis. The x-ray of pelvis showed left hip dislocation. Hypotonia, mental retardation and severe obesity may cause problems including skin necrosis, prolonged wound healing and re-dislocation after surgical treatment of hip dislocation.
Clinical management
The patient underwent open reduction, modified inverted U capsuloplasty and modified Salter osteotomy. The techniques were described previously by AE[1] After the operation the patient had a hip-spica cast to keep the hips in extension, abduction and neutral rotation. This position prevented skin necrosis. Since the patient was mentally retarded, the cast was replaced with bilateral short leg cast with abduction bar. The latter was kept for 2 months. After 2 years of follow up the patient is walking without limping.
Discussion
This is an unusual case of hip dislocation managed by a new technique. This technique can be considered in patients with severe obesity and mental retardation.
Reference
1. Eren A, Altintaş F, Atay EF, Omeroğlu H. A new capsuloplasty technique in open reduction of developmental dislocation of the hip. *J Pediatr Orthop B.* 2004 **13** 139–41.
Disclosure
The authors declared no competing interests.

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P67

McCune-Albright Syndrome in three patients, clinical correlation and spectrum of the disease

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Introduction
Albright-McCune Sternberg syndrome (SAMS) is a rare disorder which originates in a germinal mutation of gene GNAS1, which codifies the alpha subunit of protein G (Gsa). It is characterized by a typical phenotype which includes polyostotic fibrodysplasia, precocious puberty independent from gonadotropins, cafe-au-lait spots and a series of endocrine abnormalities. The most common mutations include a cysteine or histidine for arginine substitution in codon 201 of exon 8 (R201C or R201H) or a glutamine for arginine or leucine substirution in codon 227 of exon 9 (Q227L or Q227L). Woman to male relation is 10–1.
Material and methods
To describe three patients with MaCCune-Albright syndrome and a GNS1 mutation.
Results
5 year-old boy with café-au-lait spots in the face and thorax, easy fatigability, generalized osteomuscular pain, frequent sinusitis, without pubic hair and testes of 5 ml. Bone scan shows activity on both femoral bones. Low serum testosterone and no FSH or LH response to GnRH. Study by allelic specific PCR and enzymatic digestion reveal an arginine 201 to histidine mutation. The second patient is a Girl with café-au.lait spots and seriously bone fybrodi¡syplasia with compromise of her hip and cranium, She developed hyperthyroidism and seriously compromise of optic formane due to dysplasia, with severe and progressive vaginal bleeding, due to high growth velocity, analisys form gene was maden and excess of growth hormone waqs confirmed, Alendronate and Octreotide was begun with stablisatrion of cranial compromise and normalization of GH, IGF1 and growth velocity.
The third patient is a 5-years-old boy, with serioiusly compromise of left proximal femur, alendronate was started with development of adynamic bone and high values of bone densitometry, the molecular study was negative.
Analysis and conclusions
We describe three patients with the McCune-Albright syndrome and a GNAS1 mutation Two of which have with a gonadotropin independent precocious

puberty. Follow up will be important to rule out other endocrinopathies, specially growth hormone excess. Results of treatment with aromatase inhibitors, GnRH analogues or biphosphonates have not been helpful in all cases, and the diversity of evolution is presented.

Disclosure

The authors declared no competing interests.

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P68

Body composition and vertebral changes in children with osteogenesis imperfecta – effect of risedronate

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Background

Case series show improved vertebral size and shape with intravenous bisphosphonate use in children with osteogenesis imperfecta (OI); however, two studies of risedronate showed no such improvement. We have re-examined the data from a dose-ranging risedronate study to determine whether other factors, in particular relating to body composition, contribute to vertebral shape in OI.

Methods

We randomly assigned 53 children with moderate to severe OI to receive 0.2, 1, or 2 mg/kg per week risedronate for 2 years. Children naïve to bisphosphonates were recruited if they had phenotypic OI with one or more of: recurrent fractures affecting mobility; two or more crush-fractured vertebrae; or fractures causing bony deformity and requiring surgical correction. We measured body composition by DXA (GELunar Prodigy, software v4.0). Annual lateral thoracic and lumbar spine films were reviewed by three independent radiologists. Vertebrae were classified according to size and shape. Height loss was assessed as none (0–10%), moderate (10–50%) or severe (>50%). Shape was assessed as normal or showing single-end-plate, double-end-plate, or anterior-wedge deformity. Anterior wedging was the most severe deformity and single-end-plate deformity the least. Films were assessed in pairs for each child. Vertebral architecture was also globally assessed as 'improved', 'the same' or 'worse'.

Results

There was no difference in the percentage of 'improved' vertebrae between the dose groups. Weight z-score was inversely related to 'improved' vertebral architecture irrespective of treatment dose; each 1 S.D. increase in resulted in a fall of 10.3% in 'improved' vertebrae ($P=0.05$). The relationship with % change in fat mass was of a similar magnitude but did not reach significance; the opposite relationship was observed for lean mass. There was no clear relationship with risedronate dose. The number of non-vertebral fractures sustained was negatively correlated with vertebral 'improvement' ($r^2=0.22$, $P=0.003$).

Conclusions

The prevention of fractures is key to improving outcome in OI. It would appear that weight and fat mass gain may contribute to vertebral deformity. Therapeutic intervention should attend to both aspects in order to optimise patient outcome.

Disclosure

The authors declared no competing interests.

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P69

A pilot study to evaluate the effectiveness of a group circuit therapy programme for children with osteogenesis imperfecta

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Objectives

To explore the benefits of a group circuit therapy programme for children with osteogenesis imperfecta (OI) who have been identified as having functional difficulties resulting from hypermobility, reduced muscle strength, poor cardiovascular (CV) fitness and lack of engagement in physical education.

Methods

16 families were contacted to ascertain interest and preference on frequency and location for a proposed therapy group. Subsequently ten children (age range 5–13 years) participated in a 6 week movement group. Weekly 90 min sessions comprised of stations set up to replicate functional tasks which included a combination of CV fitness, strengthening, balance and fine motor tasks. Muscle strength (via hand held dynamometer), balance subscale scores (Bruininks-Oseretsky test of motor proficiency), cardiovascular fitness (difference in heart rate pre and post a 3-minute step test), number of sit ups and number of beads threaded in 1 min were collected at baseline (week 1) and following intervention (week 6). Feedback questionnaires were sent out to all participants and parents/carers at 6 weeks.

Results

Full baseline and post-intervention scores were available for five children. Mean number of sit ups completed in 1 minute improved by 100% (5 vs 10). Mean difference in heart rate (HR) before and after step test at baseline compared with post intervention was 30 beats per minute vs nine beats per minute. This drop in HR indicates a 70% improvement in CV fitness. Feedback questionnaires were received from 7/10 families including those that competed pre and post measures. These reported that 6/10 children were more active following attendance. All parents/carers appreciated the accessibility of the group and reported that their children were more confident with exercise. Post group feedback from children indicated they all felt fitter and stronger.

Conclusions

A 6 week circuit training therapy programme showed measureable improvements in fitness and core strength in children with OI. Results suggest this approach may have a range of benefits for children with OI, including improved exercise tolerance and participation in general. Further research is indicated to support these findings.

Disclosure

The authors declared no competing interests.

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P70

Ultrasonographic assessment of the skeletal development of the proximal tibia epiphysis, the proximal femur and the distal femur epiphysis in premature and mature newborns

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Backround

Usually, skeletal development and bone age in children are still examined by x-ray. In obstetrics the use of fetal ultrasonography (US) of the distal femoral epiphyseal (DFE) and proximal tibial epiphyseal (PTE) ossification centers helps to identify intrauterine growth retardation. And US has been shown to be an excellent tool to assess the mineralization of bones. First ultrasound studies were following the mineralization of bones in young infants.

Objectives

To evaluate the skeletal development of the proximal femur epiphysis (PFE), of the DFE and the PTE by musculoskeletal ultrasound in premature and mature newborns. To perform approximate age related values for the size of the ossification centers and the epiphyseal cartilage thickness.

Methods

The ossification stages of the PFE, DFE and of the PTE were determined in 180 premature and mature newborns at a biological age of 25–47 weeks in this prospective study. The size of visible ossification centers and cartilage thickness between the ossification zone and the cartilage surface in the DFE and PTE was measured. The visible onset of mineralization was recorded.

Results

The onset of visible mineralization of the DFE was recorded earliest in the 30th mature week and of the PTE earliest in the 31st mature week. The onset of visible mineralization in the PFE was earliest seen in the 43rd mature week. The mean size of the ossification centers of the DFE and the PTE (measured in two planes) was increasing by the maturity. In a comparison of three age groups (biological age 30–33 weeks, 34–37 weeks and 38–41 weeks), the mean size of the ossification centers was significant increasing ($P<0.01$). There was no significant difference between male and female newborns and between both sides.

Conclusions

MSUS is an excellent tool to follow skeletal development in premature and mature newborns. Our preliminary data of ossification center sizes and cartilage thickness emphasize that ultrasound may be an useful tool to calculate the mature age of neonates.

Disclosure

The authors declared no competing interests.

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P71

Muscle and bone impairment in children with Marfan syndrome: correlation with age and FBN1 genotype

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Background
Marfan syndrome (MFS) is a rare connective tissue disorder caused by mutation in the gene encoding the extracellular matrix protein fibrillin-1 (FBN1), leading to transforming growth factor-beta (TGF-β) signaling dysregulation. Although decreased axial and peripheral bone mineral density (BMD) has been reported in adults with MFS, data about the evolution of bone mass during childhood and adolescence are limited.
Objectives
The aim of the present study was to evaluate bone and muscle characteristics in children, adolescents, and young adults with MFS.
Patients and methods
The study population included 48 children and young adults (22 girls) with MFS with a median age of 11.9 years (range: 5.3–25.2 years). The axial skeleton was analyzed at the lumbar spine using dual-energy x-ray absorptiometry (DXA), while the appendicular skeleton (hand) was evaluated using the BoneXpert system (with the calculation of the bone health index). Muscle mass was measured by DXA.
Results
Compared with healthy age-matched controls, bone mass at the axial and appendicular levels, and muscle mass were decreased in children with MFS and worsened from childhood to adulthood.
Vitamin D deficiency (<50 nmol/l) was found in about a quarter of patients. Serum vitamin D levels were negatively correlated with age, and positively correlated with lumbar spine areal and volumetric BMD. Lean body mass (LBM) *z*-scores were positively associated with total body bone mineral content (TB-BMC) *z*-scores, and LBM was an independent predictor of TB-BMC values, suggesting that muscle hypoplasia could explain at least in part the bone loss in MFS. Patients with a *FBN1* premature termination codon mutation had a more severe musculoskeletal phenotype than patients with an inframe mutation, suggesting the involvement of TGF-β signaling dysregulation in the pathophysiologic mechanisms.
Conclusion
In light of these results, we recommend that measurement of bone mineral status should be part of the longitudinal clinical investigation of MFS children.
Disclosure
The authors declared no competing interests.

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P72

Vitamin D status in young women with anorexia nervosa during intensive weight gain therapy

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Objectives
Anorexia nervosa (AN) is a life-threatening eating disorder often associated with reduced bone mass. The aim of the present study was to investigate vitamin D status and the association with BMI, fat mass and bone mineral density (BMD) during a novel intensive nutrition therapy in young AN women.
Methods
Twenty-five female AN patients (20.1 ± 2.3 years, BMI 15.5 ± 0.9 kg/m^2) admitted to a specialised inpatient eating disorder unit were included. 11 patients had vitamin D supplements daily before study entry. Patients underwent a novel nutritional therapy during 12 weeks with an extra high-energy diet from start, median 75 kcal/kg per day, which gradually decreased to 54 kcal/kg per day over the study period. The diet contained an average of 15 μg per day vitamin D and 2120 mg per day calcium. Serum 25-hydroxyvitamin D (25 (OH) D), calcium, phosphate and parathyroid hormone (PTH) were measured. BMD and body composition were assessed by dual-energy x-ray absorptiometry (DXA) (Lunar Prodigy).
Results
22 patients completed the 12-week treatment period, and the mean weight gain was 9.9 kg and the mean BMI increased to 19.0 ± 0.9 kg/m^2, $P<0.0001$. One patient was vitamin D deficient (<25 nmol/l) and three patients had vitamin D levels <50 nmol/l at baseline. The median serum 25(OH) D was 84 nmol/l at baseline, which decreased to 76 nmol/l after 12 weeks ($P=0.033$). PTH increased from median 2.3–3.2 pmol/l ($P<0.0001$), but serum calcium and phosphate remained unchanged. Fat mass increased from median 12.4–26.7%. We found no significant associations between 25(OH) D and BMI, fat mass or total body BMD.
Conclusion
On a positive note, only one out of 25 patients was vitamin D deficient at baseline. The adequate vitamin D levels before study entry is likely caused by the widespread use of dietary supplements. The reduction in vitamin D levels during the study, despite an adequate intake, could be explained by low sunlight exposure during the treatment period and possibly due to an increased storage of vitamin D related to the increase in fat mass since vitamin D is sequestered in adipose tissue.
Disclosure
The authors declared no competing interests.

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P73

Long-term outcomes of surgical treatment for craniofacial fibrous dysplasia

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Fibrous dysplasia (FD) is a benign skeletal disease caused by somatic activating mutations of $G_s\alpha$ leading to formation of expansile fibroosseous lesions. These may occur in isolation or in association with McCune-Albright syndrome (MAS), characterized by skin pigmentation and hyperfunctioning endocrinopathies, including growth hormone (GH) excess. FD in the craniofacial skeleton may result in significant morbidity including facial asymmetry, vision and hearing loss, nasal obstruction, malocclusion, and pain. Craniofacial FD is sometimes treated surgically; however post-operative regrowth of FD tissue may result in recurrence or even worsening of craniofacial deformity.
Objectives
To determine outcomes and indications for operations and re-operations in a large cohort of subjects with craniofacial FD, and to identify risk factors for post-operative regrowth.
Methods
Clinical data from subjects in a long-standing natural history study of FD/MAS were reviewed. Surgeries were categorized as follows: debulking (partial removal and/or recontouring of FD), reconstruction (resection of FD bone with introduction of hardware and/or grafting material), optic nerve decompression, aneurysmal bone cyst enucleation, or biopsy.
Results
Of 175 patients with FD/MAS, 130 (74%) had FD involving the craniofacial skeleton. Of these, 31 (24%) underwent a total of 86 craniofacial surgeries. The distribution of surgeries was as follows: debulkings 36 (42%), reconstructions 26 (30%), optic nerve decompressions 15 (17%), aneurysmal bone cyst enucleations 9 (10%), biopsies 9 (10%). The mean length of post-operative follow-up was 13.6 years (range 0–39, s.d. 10.6). Re-operations were performed in 34 (40%) of cases. The most common indication for re-operation was FD regrowth, which occurred significantly more frequently after debulking procedures (24/36, 67%) than reconstructions (7/26, 27%) ($P=0.004$). The prevalence of MAS-associated GH excess was higher in the surgically treated group (11/31, 35%) than in patients who were managed non-operatively (16/99, 16%) ($P=0.04$). Re-operations for FD regrowth were more common in patients with GH excess (16/34, 47%) than in patients without GH excess (18/50, 36%) ($P=0.05$).
Conclusions
Post-operative FD regrowth and re-operations are common after craniofacial surgery. If surgery is undertaken, resection and reconstruction with hardware and/or grafting material may result in less regrowth and fewer re-operations than more conservative debulking and recontouring techniques. Practitioners should

be aware that MAS-associated GH excess is a risk factor for craniofacial morbidity and post-operative FD regrowth.
Disclosure
The authors declared no competing interests.
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P74

A case of resistant hypophosphataemic rickets
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Background
Hypophosphataemic rickets (HPR) is an inherited condition of phosphate wasting associated with abnormal bone biochemistry and features of rickets. Most patients respond to treatment with alfacalcidol and oral phosphate. Raised levels of alkaline phosphatase (ALP) and parathyroid hormone (PTH) generally indicate a need for refining treatment, or poor compliance.
Presenting problem
We report the case of a 36 week gestation male infant born to consanguineous South Asian parents, in whom HPR is resistant to conventional treatment. He required ventilation for bilateral choanal stenosis at 3 days of age and had craniofacial abnormalities. Direct sequencing of the FAM20C gene revealed a homozygous missense mutation in exon 6, confirming Raine syndrome. Features of this rare condition include osteosclerosis, craniofacial anomalies, choanal atresia and thoracic hypoplasia. Appositional new bone formation may resemble prenatal and postnatal fractures but HPR has not been previously described.
Metabolic bone disease
At two months, he had elevated ALP (5605 iu/l, reference range 187–1197), hypophosphataemia (0.75 mmol/l, (1.36–2.26)) and hypocalcaemia (1.92 mmol/l, (2.20–2.79)). Serum PTH was elevated (72 pmol/l, (1.1–6.9)) and vitamin D levels were suboptimal ($<$40 nmol/l). Wrist radiographs showed features in keeping with vitamin D deficiency rickets.
Clinical management
Treatment with vitamin D and calcium failed to normalize biochemistry. Analysis of urine revealed low tubular reabsorption of phosphate (72%) despite hypophosphataemia. FGF23 was raised (157 RU/ml, (0–100)), with normal 1,25 dihydroxy vitamin D, suggesting an FGF23 dependent condition akin to hereditary HPR. Treatment with increasing doses of alfacalcidol and phosphate have marginally improved bone chemistry, but PTH and ALP remain elevated at 3 years, despite normal phosphate and vitamin D levels. Radiological signs of rickets have persisted and he has recently developed nephrocalcinosis.
Discussion
Of the 24 known cases of Raine Syndrome to date, only one has been reported to have hypophosphataemia with elevated ALP.
FAM20C is known to code for the human homologue of dentin matrix protein 4 (DMP4), which is expressed in bone. It may be similar to dentin matrix protein 1 which has a role in inherited forms of hypophosphataemic rickets. Our patient has biochemical features of hypophosphataemic rickets, which has to date been resistant to conventional treatment.
Disclosure
The authors declared no competing interests.
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P75

To predict curve progression in newly diagnosed AIS girls – how good can bone mineral density do?
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Introduction and objective
Adolescent idiopathic scoliosis (AIS) is a three-dimensional spinal deformity with lateral curvature of $\geqq$10 degree measured by Cobb angle. Previous studies reported that $\sim$30% of female AIS patients had systemic osteopenia which could persist beyond skeletal maturity and that was one of the important prognostic factors. The aim of this study is to investigate the incremental prognostic value of osteopenia on curve progression in AIS as defined by Scoliosis Research Society (SRS) criteria using the decision curve analysis (DCA) and reclassification table.
Methods
Between 1997 and 2014, 450 newly diagnosed AIS girls aged 11–16 years old before skeletal maturity without prior treatment and with initial Cobb angle $\leq$40° were recruited. Bilateral hips were measured by dual-energy x-ray absorptiometry (DXA) at their initial clinic visit, followed by regular follow-up with detailed clinical and radiological assessments. Curve progression was defined as $\geqq$6° increase at maturity (years since menarche$\geqq$2 and age$\geqq$16). Two regression models were compared in their prediction on curve progression. Model 1 (M1) included background variables of Cobb angle, age at clinic, menarche status (yes/no) and assigned brace treatment (yes/no) at first visit. Model 2 (M2) was same as M1 added with the osteopenia status (yes/no) using z-score of bone mineral density (BMD).
Results
Among all subjects, 92 (20.4%) were osteopenia with z-score of BMD≤ -1 at femoral neck and 72 (18.7%) had curve progression (progressive cases), as defined by SRS criteria. Overall, M2 has better performance than M1 (AUC 0.641 vs 0.631, $P=0.568$, Nagelkerges R^2 0.068 vs 0.052, $P=0.035$). DCA showed similar results (M2 had higher net-benefit values than M1). Besides, M2 improved the reclassification of high-risk progressive cases when compared to M1 (net reclassification improvement$=0.123$, $P=0.003$), e.g. $\sim$12.3% better classification by including baseline osteopenia status in prediction model.
Conclusion
In conclusion, the prediction model with baseline osteopenia had better prediction performance than that of without. Despite reaching statistical significance, the relatively low value of R^2 indicates the presence of other bone health parameters that might have to be included to further improve the predictive power for curve progression.
Disclosure
The authors declared no competing interests.
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P76

Bone quality in severe adolescent idiopathic scoliosis – quantitative computed tomography of lumbar spine vs high-resolution peripheral quantitative computed tomography of the distal radius: a pilot study
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Introduction and objective
Adolescent idiopathic scoliosis (AIS) is a structural spinal deformity characterized by 3D deformity with lateral curvature of $\geqq$10° as measured by Cobb angle and is predominately seen in girlsaged between 10 and 16-years-old. Low bone mass has been found to be a significant prognostic factor for curve progression in AIS.
In our hospital, computed assisted navigation is used for intraoperative pedicle screw placement which will require pre-operative CT of whole spine. A set of calibration phantoms was used in all preoperative CT scanning so that the attenuation measured in the bone can be converted from Hounsfield units (HU) to bone mineral equivalents in mg/cm^3. Both quantitative computed tomography (QCT) and high-resolution peripheral quantitative computed tomography (HR-pQCT) allow the study of cortical bone and trabecular bone separately and enable to acquire three-dimensional (3-D) volumetric BMD of each compartment. The objective of this study is to correlate the volumetric bone mineral density (vBMD) of central and appendicular skeleton using QCT and HR-pQCT.
Methods
In this pilot study, eight AIS girls aged 13–18 with planned operation (Cobb angle$>$45°) were recruited. Lumbar spine L1–L2 and non-dominant distal radius were measured by QCT and HR-pQCT respectively.
Results
The mean age was 15.6$\pm$2.2 years old and the mean Cobb angle was 62°$\pm$15°. Of the eight patients, 3 (37.5%) were osteopenia with z-score of femoral neck ≤ -1. Using the Pearson correlation, significant correlation of the L1 vertebra and distal radius were found including the total vBMD ($P=0.021$), cortical vBMD ($P=0.026$) and trabecular vBMD ($P=0.018$). Besides, trabecular vBMD of L2 vertebra was significantly correlated with that of distal radius ($P=0.021$).

Conclusion
In conclusion, in this pilot study, the bone quality measured by QCT at L1 vertebra (central skeleton) was well correlated with that of HR-pQCT at non-dominant distal radius (appendicular skeleton). Further studies with larger number of patients should be carried out in the future to validate the findings which could provide better prognostication of curve progression and improve our understanding of the etiopathogenesis of AIS.
Disclosure
The authors declared no competing interests.
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P77

Vertebral fractures in children affected by chronic recurrent multifocal osteomyelitis: case reports and therapy response

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Chronic recurrent multifocal osteomyelitis (CRMO) is a rare, auto-inflammatory disorder of unknown cause that affects children and adolescents. CRMO is characterized by periodic bone pain, fever, multiple bone lesions occurring at any skeletal site, even if the metaphyseal area of long bones, clavicle and shoulder girdle are the most common locations. Dermatological manifestations include psoriasis, acne and pustules. The clinical and radiological features of the disease are variable and diagnosis can be difficult. Medical management includes nonsteroidal anti-inflammatory drugs, oral steroids and immunosuppressive drugs.
Two previously healthy boys, 13-year old (case 1) and 9-year old (case 2), with a recent diagnosis of CRMO, were referred to our department for a deeper evaluation of calcium metabolism and bone mineralization.
Case 1 had back pain, difficulty walking, and osteolytic lesions at right ulna and right trochanteric region. Case 2 had back pain, difficulty walking, skin lesions (pustules) on right leg, and osteolytic lesions at left femur and dorsal spine.
Both boys had been treated with oral steroids in the previous months with reduction of the osteolytic lesions.
Serum calcium, phosphate, magnesium, PTH and 25-OH vitamin D were normal for age. Phosphaturia was normal, calciuria was reduced. Bone turnover markers were moderately increased for age. Thyroid and gonadic function were normal. No other laboratory abnormalities were found.
Spine x-ray and MRI showed the presence of vertebral fractures: T_4 and T_6 in case 1; T_5 and T_6 in case 2.
Bone mineral density (BMD): case 1, spine z-score -0.6, femoral z-score -1.2 and total-body less head (TBLH) z-score -1.3; case 2, spine z-score -3.2; femoral z-score -2.1 and TBLH z-score $-1,8$.
Considering the presence of vertebral fractures, intravenous pamidronate (0.5 mg/kg, threee infusions in a week, once every 3 months) was started. After the second cycle, there was an improvement in both patients: pain disappeared, bone lesions and vertebral fractures stabilized, and walking was normalized.
A longer follow-up is needed to see the long-term effect on the disease and bone involvement (fractures and BMD).
Disclosure
The authors declared no competing interests.
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P78

Bone metabolism in children and adolescents with newly diagnosed acute lymphoblastic leukemia

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In children and adolescents with acute lymphoblastic leukemia (ALL), low bone mineral density (BMD) and increased risk of fractures can be observed at diagnosis and/or during treatment.
This prospective study was aimed to evaluate BMD and bone turnover in patients with a new diagnosis of ALL, treated with an international protocol (AIEOP BFM ALL 2009) (*), based on high-dose steroids and chemotherapeutic drugs.
Inclusion criteria were age 3–18 years, no other diseases, no previous use of steroids or chemotherapy.
During 15 months, out of 54 children and adolescents consecutively diagnosed with ALL, 30 subjects were enrolled in the study (median age 8 years; 13 males; eight pubertal).
We present the preliminary results on bone mineral density (BMD, measured by dual-energy x-ray absorptiometry), and bone turnover markers (C-terminal telopeptide (CTx), osteoprotegerin (OPG), receptor activator of nuclear factor kappa-B ligand (RANKL)), at baseline and at start of the reinduction phase (about 6 months after diagnosis).
At baseline, the mean level of 25-OH vitamin D was 17 ng/ml (normal in 41.3% of patients, low in 58.7/%), and one previous appendicular fracture was reported by one patient.
During the study, CTx serum levels increased from 906.7 pg/ml (baseline) to 1.485 pg/ml (reinduction phase) ($P=0.005$). The RANKL/OPG ratio (probably investigated for the first time in pediatric ALL) was higher than normal, but decreased from baseline to reinduction phase (baseline 59.2; reinduction 38.1; normal 28 ± 11).
Bone mineral apparent density (BMAD) z-score at lumbar spine and BMD z-score at total body less head (TBLH) were already decreased at baseline in 46.7 and 22% of children respectively, and continued to decrease during therapy, especially TBLH ($P=0.006$). Five patients had sustained one incident appendicular fracture by start of reinduction phase.
In conclusion, imbalance of RANKL/OPG system, with consequent low values of spine and total body BMD and increased bone resorption were present at diagnosis and during the first 6 months of treatment in children and adolescents with ALL. Further studies are needed to confirm these findings.
(*) AIEOP = Associazione Italiana di Ematologia Oncologia Pediatrica; BFM = Berlin Frankfurt Muenster.
Disclosure
The authors declared no competing interests.
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P79

Nonbacterial osteitis: Is there any mismatch in the pathophysiology of osteoblasts or osteoclasts?

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The aim of the study is to determine whether there is an imbalance between bone formation and bone resorption in nonbacterial osteitis. The osteoclast inhibitor pamidronate has been successfully used in nonbacterial osteitis. It is assumed, that there is any mismatch in the pathophysiology of osteoblasts or osteoclasts. Until now, we have no known publications on bone metabolism in nonbacterial osteitis.
We chose osteoprotegerin (OP) and alkaline phosphatase (AP) as markers of bone formation and dickkopf-1 (DKK-1) and cathepsin k as markers of bone resorption.
The serum levels of osteoprotegerin, alkaline phosphatase, dickkopf-1 and cathepsin k were measured in 55 patients, in 7–25 years of age, using enzyme link immunoassay test. We compared the serum levels of OP, DKK-1 with an average value of a healthy control group from the literature.
74% of patients had low levels of OP in comparison to normative data. All patients had lower levels of DKK-1. A significant difference in levels of DKK-1 was observed between patients who didn't receive pamidronate or etanercept during the observation period and patients who needed these drugs in the course of disease ($P=0.023$). No significant difference was found by OP ($P=0.592$). AP was in the normal range. Serum level of cathepsin k was just detecting in one patient.
They weren't significant results by OP and DKK-1 in follow groups: unifocal vs multifocal bone lesions (OP $P=0.05$, DKK-1 $P=0.861$), with vs without hyperostosis (OP $P=0.863$, DKK-1 $P=0.544$), high vs no high serum levels of TNF-α (OP $P=0.768$, DKK-1 $P=0.547$), axial vs no axial involvement (OP $P=0.993$, DKK-1 $P=0.186$), vertebral body involvement vs no vertebral body involvement (OP $P=0.241$, DKK-1 $P=0.505$).
Patients with nonbacterial osteitis had a low turnover in bone remodeling. Patients with a serious course of disease may have more osteoclast activity than other patients in terms of DKK-1 levels.

Disclosure
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P80

Ibandronate in the treatment of pediatric osteoporosis

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Objectives
To evaluate the effect of oral ibandronate on bone health in osteoporotic children and adolescents, as there are only scarce data regarding its use in pediatric population.
Patients, materials, methods
We enrolled seven patients (six boys; one girl; mean age 15.3±3.8 years; range 8–18 years) with low bone mineral density (BMD) (mean 0.746±0.141 g/cm^2; i.e. −3.3±1.5 S.D. *z*-score) and with prevalent low-energy trauma fractures (mean 4.0±4.2 S.D.). Oral ibandronate (150 mg per tablet) was administered once-a-month in full accordance with current recommendations. All patients were receiving oral calcium (1000–1500 mg per day) and vitamin D (cholecalciferol, 1000–1500 IU per day). Laboratory parameters (biochemical: S-Na, K, Cl, Ca, P, ALP, AST, ALT, urea nitrogen, creatinine, parathyroid hormone; bone markers: S-osteocalcin, Crosslaps; hematologic – blood count) were assessed on baseline and were further checked every three months within the first year of therapy, and every 6 months thereafter. Lumbar spine BMD was assessed by DXA (Lunar in seven subjects and Hologic in one) at the baseline and every 12 months of the treatment. New fractures and adverse events were recorded in the course of the treatment.
Results
Mean duration of the treatment was 2.0±0.8 years: 1 year (n=2 patients), 2 years (n=3), 3 years (n=2). In one patient the treatment is still ongoing. After 1 year there was a mean 17% increase in BMD (0.866±0.118 g/cm$^{2;}$ *z*-score −2.2±1.4 S.D.; P=0.0003), after second year of treatment there was additional mean 3% increase in BMD (0.920±0.057 g/cm^2; *z*-score −2.1±2.0 S.D.; P=0.4); P=0.001 compared to baseline values.The two subjects who completed three years' treatment had mean additional 9% increase in BMD. The baseline values of laboratory parameters were within reference ranges and remained such in the course of the treatment. No new fractures occurred. Only one adverse event/reaction was recorded in one subject: transient epigastric pain and myalgia after the first dose of ibandronate. None of the patients experienced dental problems.
Conclusion
Orally administered ibandronate significantly increased BMD and decreased fracture incidence in pediatric patients with osteoporosis. Oral ibandronate can be helpful in the treatment of pediatric osteoporosis.
Disclosure
The authors declared no competing interests.
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P81

Liver growth hormone receptor signaling in chronic kidney disease related growth retardation: the role of suppressor of cytokine signaling 2

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Introduction
Children with chronic kidney disease (CKD) who suffer from growth retardation have usually normal circulating GH but low IGF1, suggesting GH resistance. We have previously shown in growth retarded CKD rats an increase in suppressor of cytokine signaling 2 (SOCS2) levels, a key negative regulator of GH signaling. SOCS2 spontaneously mutated (HG) mice show an exaggerated body growth and increased bone mass. We investigated growth and GH receptor (GHR) signaling in liver tissue of uremic SOCS2 deficient mice.
Methods
4-week old HG and normal wild-type mice (N) underwent 5/6 nephrectomy (CKD) or sham operation (C), forming four groups: C-N, C-HG, CKD-N, CKD-HG. Mice were sacrificed after 3 weeks (3W) or 12 weeks (12W) after disease induction. A single IP bolus of bovine GH was given 30 min before sacrifice.
Results
CKD-N and CKD-HG mice had similar degrees of renal insufficiency. Weight gain was reduced significantly in CKD-N vs C-N, but increased significantly in C-HG & CKD-HG. Liver SOCS2 mRNA, totally absent in HG mice, was increased in CKD-N vs C-N. Liver GHR protein levels were similar in all groups, excluding an elevation in the C-HG group after 12W. GH stimulated STAT5 phosphorylation decreased in CKD-N vs C-N in both time points and increased in CKD-HG vs CKD-N only after 3W but not after 12W. IL6 and SOCS3 mRNA, and phospho-STAT3 (a signal downstream of IL6) increased in CKD-HG after 3W. Phospho-STAT3 increased in C-HG, CKD-N and CKD-HG vs C-N further increasing in C-HG. SOCS3 increased in CKD-N and IL6 increased in CKD-HG, further increasing in C-HG after 12W.
Conclusions
CKD SOCS2 mutants exhibit an improved somatic growth without worsening of CKD phenotype. A single bolus of GH prior to sacrifice induced a depressed phosphorylation of liver STAT5 in CKD-N vs an actual increase in CKD-HG mice, supporting the central role of SOCS2 in regulating GHR signaling. The IL6 and STAT3 increase in CKD-N & CKD-HG and the SOCS3 increase in CKD-N group suggest that low grade inflammation also contributes to negative GHR signaling in CKD, even if SOCS2 is deficient.
Disclosure
The authors declared no competing interests.
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P82

Relationships among 25-hydroxyvitamin D, Parathyroid Hormone, and bone turnover markers in Chinese children

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Background
Vitamin D status is associated with bone health. Vitamin D deficiency leads to decreased bone formation and increased bone resorption. 25-hydroxyvitamin D (25(OH) D), parathyroid hormone (PTH) levels in children could affect bone turnover, and in turn, the bone markers should reflect vitamin D condition. In children the relationships among 25(OH) D, PTH and bone turnover markers are remain.
Objective
To explore the associations among serum 25(OH) D, intact-parathyroid hormone (iPTH) and bone turnover markers in Chinese children; to observe the changes of serum 25(OH) D, iPTH and bone turnover markers along with age.
Methods
Data were collected during summer December, 2012 and March, 2013 in 85 boys and 65 girls who came to Division of Nutrition, Growth and Development & Endocrinology of Department of Pediatrics, Second Hospital of Hebei Medical University for health examine. Measurements included serum 25(OH) D, iPTH, osteocalcin (OC), alkalinephosphatease (ALP), bone alkalinephosphateasecollagen (BAP), calcium (Ca), phosphorus (P) and urine deoxypyridinoline (DPD), urine creatinine (Cr) and dietary intake of vitamin D and calcium, sunlight exposure, height, weight and BMI.
Results
i) According to serum 25(OH) D levels, children were divided into four groups like <27.5 nmol/l, 27.5–50 nmol/l, 50–75 nmol/l and >75 nmol/l groups. We found serum OC levels decreased along with the increased 25(OH) D levels. All the subjects were grouped based on serum iPTH levels as <1 pmol/l, 1–1.5 pmol/l, 1.5–2 pmol/l and >2 pmol/l. We found OC and BAP levels increased obviously along with the increased iPTH levels. ii) The relevancies between 25(OH) D, iPTH and bone metabolism markers were analyzed by spearman correlation test. Serum OC was negatively related to 25(OH) D (R=−0.445, P<0.001) and positively related to iPTH (R=0.242, P=0.003). Serum BAP and ALP were both positively related to iPTH (R=0.3, P<0.001;

$R=0.291$, $P<0.001$). There was obviously positive relation between serum ALP and BAP of children either in different age or different gender. There were no obvious relations among other markers. iii) The urine-DPD levels were higher in infants & toddlers than school age & adolescents; serum OC levels were higher in school age & adolescents than infants & toddlers.
Conclusion
i) Serum 25(OH) D and iPTH are closely related to bone turnover markers, however it is not clear whether to assess the suitable 25(OH) D level by bone turnover markers. ii) Serum 25(OH) D and bone turnover markers were different in different ages in Chinese children.
Disclosure
The authors declared no competing interests.
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P83

RANKL, OPG, Dkk1 in Duchenne muscular dystrophy
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Low bone mineral density (BMD) and an increased rate of both peripheral and vertebral fractures have been observed in patients with Duchenne muscular dystrophy (DMD). However, studies specifically addressing bone metabolism, BMD and fractures in this disease are still very few.
Our ongoing multicenter, prospective study is aimed to identify the characteristics of the DMD boys with a higher risk of bone loss and fractures, through the evaluation of bone turnover, BMD, and genetic configuration.
We studied a group of 37 DMD boys (mean age 10.6 ± 3.2 years), and are now presenting our preliminary findings, at baseline, on BMD (measured by dual-energy x-ray absorptiometry), serum osteoprotegerin (OPG), receptor activator of nuclear factor kappa-B ligand (RANKL) and Dickkopf-1 (Dkk1) (evaluated for the first time in DMD boys).
In these patients, at baseline, the RANKL/OPG ratio was significantly higher than normal, while Dkk1 was lower (see Table 1). 28 patients (75.7%) had a significantly reduced spine bone mineral apparent density (BMAD) (z-score ≤ -2).

Table 1

	RANKL/OPG ratio	Dkk1 pmol/l	*P*
DMD subjects	112.3 ± 107.2	17.44 ± 17.1	<0.001
Normal values	28 ± 11	37 ± 18.3	<0.02

A significant correlation was observed between Dkk1 levels and BMAD z-scores ($P<0.005$) and also between RANKL/OPG ratios and BMAD z-scores ($P=0.03$). The imbalance between RANKL and OPG, and the insufficient compensation provided by the reduction of Dkk1, may suggest a possible explanation of the low BMD and increased fragility and fracture risk in boys affected by DMD. Further studies are needed to confirm this hypothesis.
Disclosure
The authors declared no competing interests.
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P84

Different causes of infantile hypercalcemia
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Background
Hypercalcemia in childhood is rare, can be of various origin and might go unrecognized until severe signs appear. We demonstrate hypercalcemia of different causes in two infants.
Case no 1.
5-month old girl with failure to thrive, constipation, muscle hypotonia, dehydration, where total calcaemia peaked to 4.25 mmol/l. Low calcium diet, application of glucocorticoids and furosemide resulted in a drop in calcaemia to values below 3 mmol/l and in an overall clinical improvement within 2 weeks. Williams-Beuren syndrome (WBS), benign familial hypocalciuric hypercalcemia (FHH), neonatal severe primary hyperparathyroidism (NSHPT), Jansen's metaphyseal dysplasia, primary hyperparathyroidism, vitamin D intoxication, granulomatous diseases, thyroid disease, malignancy were all ruled out. The diagnosis of idiopathic infantile hypercalcemia (IIH) was established. CYP24A1 inactivating mutation p.R396W+L409S (c.1186c>t)+(c.1226t>c) was later identified in this patient, thus confirming the diagnosis IIH. Currently the girl is 10-years-old, with normal anthropometric parameters and normal values of serum and urinary calcium.
Case No. 2
A 7-month old girl with normal perinatal history was referred due to lethargy, anorexia, failure to thrive, psychomotor retardation, muscle hypotonia. Blood biochemistry revealed high levels of serum calcium (S-Ca, 3.5 and 3.8 mmol/l respectively) with low parathyroid hormone (S-PTH) concentration (4.8 ng/l; normal 15–65), and otherwise normal lab results Echocardiography was normal, with no signs of aortal or pulmonary artery stenosis. A diagnosis of idiopathic infantile hypercalcaemia was first established and girl received intravenous corticosteroids and oral furosemide together with adequate hydration and low-calcium diet. This resulted in a drop in S-Ca (3.02 mmol/l) after 2 days of treatment. She then received a milk-free diet without vitamin D supplementation. Calcemia was in the range of 2.25–2.5 mmol/l. Her psychomotor development and muscle hypotonia have been improving very slowly in comparison with the drop in S-Ca and her weight gains were inappropriately low. She had no striking dysmorphic features, however, the persisting psychomotor retardation and failure to thrive prompted us to have FISH (fluorescent *in situ*hybridization) performed. The FISH revealed deletion at the long arm of chromosome 7, thus arriving at the diagnosis of WBS. Currently, the girl is 6 years old, mildly retarded, being followed up in our ward. Typical facial features of WBS have since evolved.
Conclusion
Disturbances of calcium homeostasis have to be considered in the differential diagnosis of various disease states., especially in infants with failure to thrive.
Disclosure
The authors declared no competing interests.
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P85

Comparison of three detection assays of serum 25(OH) D
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The skeletal effects and new biological effect of Vitamin D are receiving increased attention. However detection methods in 25-hydroxyvitamin D (25(OH) D) measurement are not standardized and variation between laboratories ahd methods has become attractive. This study emphasizes relativity and consistency between ELISA, ESI-LC-MS/MS and electrochemical luminescence analysis which are used widely in China. This study collected 64 cases of blood, and finally obtained good relativity and consistency in every two assays, especially between ELISA and ESI-LC-MS/MS, through linear regression analysis and Bland-Altman analysis. Chinese laboratories can choose any one from the three assays according to its own condition. This study provides the reference for vitamin D deficiency, excess assessment and monitoring as well as optimal level exploration in China.
Disclosure
The authors declared no competing interests.
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P86

Caries intensity and bone mineral density in children living in fluorine deficient region

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Objectives
Evaluation of influence the structural and functional condition of bone tissue on caries intensity in adolescents living with deficient of fluoride in drinking water (<0.4 mg/l).
Methods
It was examined 200 school children (12 and 15 years old) living in Transcarpathian region.
Oral examination was done to determine caries intensity in the subjects (DMFT-index). Bone quality was determined using quantitative ultrasound densitometry and included the following parameters: speed of sound (SOS), broadband ultrasound attenuation (BUA), and stiffness index (SI), and bone mineral density (BMD) index.
The data were acquired, computed and statistically analyzed to compare the correlation between the sources of bone mineral density and caries intensity.
Results
The studies had found statistically significant increase of DMFT index with age in children of both sexes: in girls in 12 it was 5,0 (4.0; 10.0), in 15–10.0 (7.0; 13.0) and in boys–6.0 (4.0; 7.0) and 10.0 (6.5; 12.0) respectively ($P<0.001$).
By studying the characteristics of ultrasonic bone mineral density identified the following patterns: 12-year olds girls compared with boys had higher values of SOS–1559.2 (1545.8; 1572.3) to 1546.5 (1538.4; 1557.6), $P<0.005$; SI–94.39 (86.68; 100.5) to 89.22 (82.99; 96.93), $P<0,05$; BMD index – 0.52 (0.47; 0.56) to 0.49 (0.45; 0.54), $P<0.05$ and in 15-year-old girls–indicators of SI 95.17 (87.3; 101.48) to 90.15 (81.9; 100.01), $P<0.05$; BMD index – 0.52 (0.47; 0.56) to 0.49 (0.44; 0.56), $P<0.05$.
Low bone mass was observed in 2.27% (95% CI: 3.95; 19.58) 12-year-old girls and 9.09% (95% CI: 3.95; 19.58) 12-year-old boys; among 15-year-old children–in girls: 3.64% (95% CI: 0.44, 13.14) and in boys: 13.64% (95% CI: 6.4; 26.71).
It was found statistically significant negative correlation in 12 years girls between caries intensity and SOS (Spearman correlation coefficient (R), $R=-0.47$; $P<0.01$), BUA ($R=-0.39$; $P<0.005$), SI ($R=-0.47$; $P<0.005$), and BMD ($R=-0.47$; $P<0.005$). Also in 15-year-old children found moderate negative correlation between DMFT and SOS: in girls ($R=-0.25$, $P<0.05$), in boys ($R=-0.34$, $P<0.05$).
Conclusion
Low bone mineral density can be considered as one of the important factor to increase the caries intensity.
Disclosure
The authors declared no competing interests.

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P87

Influence of vitamin D deficiency on the bone mineral density in schoolchildren

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Introduction
The recent studies show high prevalence of vitamin D deficiency and insufficiency all over the world. Vitamin D deficiency can cause serious problems such as rickets in children and osteomalacia in adults.
The aim of the study was to determine the influence of vitamin D deficiency on bone mineral density.
Methods
There were examined 304 children aged 10–18 years. The boys consisted 53%. The average age of boys was 13.2 ± 0.2 and girls – 13.2 ± 0.2 years old. Bone mineral density was examined by ultrasound densitometry of calcaneus (SAHARA, Hologic). 25(OH) D and iPTH in blood serum were determined by electrochemiluminescence method (Elecsys 2010, Roche).
Results
Vitamin D deficiency was founded in 88.5% of schoolchildren, and vitamin D insufficiency was diagnosed in 8.9% of cases. Secondary hyperparathyroidism was verified in 0.9% of children.
Children with vitamin D insufficiency had significantly higher data of ultrasound densitometry data in comparison with schoolchildren with severe vitamin D deficiency: stiffness index 105.03 ± 6.12 vs 93.70 ± 2.51 ($P<0.02$); BMD 0.574 ± 0.024 vs 0.528 ± 0.019 ($P<0.02$) and SOS 1573.6 ± 6.7 vs 1557.2 ± 5.4 ($P<0.01$). Only 12–15 years old children had negative significant correlation between iPTH and ultrasound densitometry data: correlation between iPTH and stiffness index was $r=-0.19$, $P=0.01$, BMD and iPTH – $r=-0.23$, $P=0.01$, BUA and iPTH – ($r=-0.19$, $P=0.05$).
Conclusion
Vitamin D deficiency leads to secondary hyperparathyroidism and can be the reason of low bone mass in schoolchildren of 12–15 years old.
Disclosure
The authors declared no competing interests.

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P88

Vitamin D and bone health: A practical clinical guideline for management in children and young people in the UK

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Background
There is currently considerable clinical and academic interest in vitamin D in children and young people. This partly relates to recognition of a resurgence of symptomatic vitamin D deficiency with reports of children presenting with rickets or hypocalcaemic symptoms. An additional development has been the recognition that vitamin D may have a physiological extraskeletal role beyond its traditional function as a key regulator of calcium and bone metabolism.
Presenting problem
There is recognition that many individuals have suboptimal vitamin D status often without symptoms. One response has been a large increase in requests for measurement of vitamin D (typically serum 25OH vitamin D (25OHD)). Lack of consensus and national guidance has contributed to variation in clinical practice in the UK in terms of both testing and vitamin D treatment in children and young people.
Clinical management
Guidelines for investigation and management of vitamin D deficiency in children and young people have been produced to guide clinicians in the UK. Consistent with other UK and European guidelines, the following definitions are used:

- Serum 25OHD <25nmol/l is deficient.
- Serum 25OHD of 25-50nmol/l may be inadequate in some people.
- Serum 25OHD >50nmol/l is sufficient for almost the whole population.

The guideline recommends:

- Measurement of serum 25OHD as the best way of estimating vitamin D status.
- Testing of serum 25OHD levels should be restricted to children and young people in whom there is a clear indication.
- Primary preventive measures should be undertaken in patients at high risk of deficiency. This would include advice about safe sunlight exposure, dietary sources of vitamin D and multivitamin supplementation.
- Treatment of vitamin D deficiency should be with oral preparations of vitamin D_2 or D_3 given daily for 8–12 weeks.
- Many children with vitamin D deficiency will benefit from advice about dietary calcium intake.

Discussion
By publishing these guidelines we aim to provide a useful resource that will benefit patients and families, support doctors and help to ensure that finite NHS resources are appropriately targeted. The full guideline can be accessed online at: www.nos.org.uk/professionals.
Disclosure
Dr Arundel and Dr Shaw have both provided consultancy to Consilient Health Ltd who manufacture vitamin D preparations.

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P89

Bone mineral density in solid cancer survivors: a cross sectional long-term follow-up study. A preliminary report

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Objectives
Abnormal bone mass is one of the late effects which might affect childhood cancer survivors in their later life. There are a lot of studies assessing bone deficits in patients with blood cancer, however there is little research conducted on solid cancer survivors. The aim of this study was to determine the frequency of low bone mass in analyzed group and to assess the influence of time after the end of treatment.
Methods
A cross-sectional study was conducted in a cohort of 19 patients after anticancer treatment (ten girls, nine boys) treated for solid tumors (Wilms tumor, soft tissue sarcoma, germ cell tumor and neuroblastoma) in 1985–2004 in north-eastern region of Poland. Bone mineral density was determined using dual-energy x-ray absorptiometry (DXA) at two time points after completion of treatment: 1 – from 1–5 years (mean age; 10.42 ± 3.56 years), 2 – above 5 years (mean age: 15.58 ± 3.58 years). *z*-scores below 2.0 S.D. were referred to as low bone mass, in keeping with the reference population and current practice guidelines (ISCD). Statistical analysis was performed using Wilcoxon rank sum test.
Results
Low bone mass was found in six patients (31%) at the first time point and two patients (10%) in the second study. Analysis for paired observations did not show any significant differences in time for bone mineral composition, Total bone mineral density and Lumbar spine bone mineral density (1.421 ± 0.39 vs 0.307 ± 0.63; -0.913 ± 1.55 vs -0.296 ± 0.93; -0.257 ± 1.65 vs -0.628 ± 1.15, $P < 0.05$ respectively). There were no clinically significant fractures among patients with low bone mass.
Conclusion
Childhood solid cancer survivors demonstrate bone deficits especially less than 5 years after end of treatment. However, this specific group requires longitudinal multi-centers investigation to assess the pattern of peak bone mass achievement and the risk of future bone loss.
Disclosure
The authors declared no competing interests.

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P90

Longitudinal bone development in patients with classical congenital adrenal hyperplasia: data using peripheral quantitative computed tomography

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Background/aims
Glucocorticoid treatment may influence bone and muscle development in patients with congenital adrenal hyperplasia (CAH). This study evaluates bone mineral density (BMD), bone geometry and muscle mass longitudinally throughout childhood.
Methods
Eighteen patients (ten males, eight females) with classical CAH were included. BMD, bone geometry and muscle mass were measured using peripheral quantitative computed tomography (pQCT) in prepubertal, midpubertal and postpubertal years.
Results
Mean age at first measurement was 9.70 ± 1.95 years, at second 13.94 ± 0.98 years and at third 17.03 ± 1.11 years respectively. The corresponding bone ages were within a range of ± 1 years for chronological age. In all, mean S.D. score for trabecular BMD decreased (from 0.77 ± 1.24 to -0.32 ± 1.12), whereas mean cortical BMD increased (from -0.40 ± 1.39 to 0.74 ± 1.18). Mean SD scores at first measurement for total (0.86 ± 1.12) and medullary cross-sectional area (CSA) (2.10 ± 1.17) were significantly elevated, also at all further time points, but decreased with time ($\Delta -0.802$ and $\Delta -0.61$ respectively; $P < 0.001$). In all patients, S.D. score for relative cortical CSA (-1.32 ± 01.16) was stable on a reduced level throughout childhood. After adjustment for lower height, muscle CSA was normal in all.
Conclusion
From childhood to adolescence we observed a reduction of trabecular BMD. There is an enlarged total and medullary CSA in CAH patients that decrease with time. Relative cortical CSA was reduced in all CAH patients. These longitudinal changes in bone geometry may have a long-term impact on bone stability.
Disclosure
The authors declared no competing interests.

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Changes in the concentration of vitamin D in the course of intensive treatment of acute lymphoblastic leukemia. A preliminary data

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Objectives
Children during the intensive treatment of cancer might be exposed to vitamin D deficiency and consequently leads to, among other things, bone deficits and low bone mass. The aim of this study was: i) to assess the serum concentration of 25-hydroxyvitamin D (25-OH-D) in children diagnosed with acute lymphoblastic leukemia (ALL) at two time points (time of diagnosis and just after induction treatment), ii) to evaluate the impact of used drugs on the changes of 25-OH-D concentration in the first phase of ALL treatment.
Methods
Blood samples were obtained for 27 children treated for ALL (17 boys, ten girls) in 2013 to 2014 in north-eastern region of Poland. Assessment of 25-OH-D concentrations were carried out before start of treatment and just after end of intensive therapy (at the beginning of maintenance treatment). Statistical analysis was performed using Wilcoxon rank sum test.
Results
Median age at diagnosis and after intensive treatment was 3.15 and 3.84 years respectively. 44% were vitamin D-insuficient (20–30 ng/ml) while 44% were vitamin D-deficient (level <20 ng/ml), only three patients (12%) had a sufficient level of 25-OH-D. Analysis for paired observations did not show any significant differences in time for mean concentration of 25-OH-D (22.67 ± 10.8 vs 23.9 ± 10.1; $P < 0.05$).
Conclusion
The prevalence of 25-OH-D insufficiency or deficiency in children diagnosed with ALL is high. It seems that the intensive phase of ALL treatment do not influence on level of vitamin D. However, further studies in this field is needed.
Disclosure
The authors declared no competing interests.

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Risedronate in the treatment of children with osteogenesis imperfecta: retrospective review of practice and outcomes at a large paediatric metabolic bone unit

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Objectives and method
We retrospectively reviewed records of current patients with osteogenesis imperfecta (OI) to identify those on risedronate, doses used and effects of treatment. BMD changes over time were calculated as difference between measurement before risedronate and at one year (including measurements −3–0 m and 10–14 m after starting risedronate respectively).
Results
219/296 (74%) patients with OI had received bisphosphonates (median 10.92 years; 0.43–19.15). 73/296 (25%) had received risedronate; median starting age 10.21 years (3.76–16.99). 62/73 were started on purely clinical grounds (study patients excluded). 58/62 had mild/moderate OI. Clinical use is increasing (27/62 started in last 2 years).
50/62 were on pamidronate before risedronate; median age starting risedronate 12.35 years (4.1–16.99); mean duration pamidronate 7.1 years (1.14–15.89). Mean pamidronate starting dose was 11.8 mg/kg/year (35/36 on 12 mg/kg/year); reduced to 7.17 mg/kg/year over 12 months before switch to risedronate. 11/61 were bisphosphonate-naive when starting risedronate; most common indication was multiple vertebral fractures (n = 8/11).

Mean starting dose of risedronate was 0.95 mg/kg/week (0.34–2.13). Over first 12 m risedronate treatment, mean z-score and % changes in L2–L4 BMD were +0.25 (CI +0.03 to +0.47) and +10.31% (CI 5.88–14.74%), respectively ($n=15/61$). Mean starting dose was greater in bisphosphonate-naive (1.38 mg/kg/week; 0.97–2.13) than pamidronate-exposed group (0.86 mg/kg/week; 0.34–1.84)($P=0.001$). Increase in L2–L4 BMD (z-score; % change) over 12 m after starting risedronate was greater in bisphosphonate-naive (+0.68; 18.99%) than pamidronate-exposed group (+0.10; 7.15%).
Risedronate was discontinued in 14/61; 5/14 stopped for possible adverse effects (4/5 gastrointestinal upset, 1/5 hair loss). 2/14 temporarily discontinued for poor osteotomy healing and following proximal femoral fracture.
Weight-adjusted dose was inversely proportional to age ($r^2=0.33$; $P<0.0001$). L2–L4 BMD z-score increase over 12 m was directly proportional to dose (intercept 0.8 mg/kg/week; $r^2=0.44$; $P=0.01$). There is no significant relationship between age and change in z-score ($P=0.06$) or % change in L2–L4 BMD ($P=0.50$) over first 12 m of treatment ($n=15/61$).
Conclusion
Risedronate use has increased in our unit, principally as a substitute for pamidronate in later childhood. Weight-adjusted dose correlated with age, probably due to the preparation available. Doses used and L2–L4 BMD increases are consistent with published studies. We believe there is a place for risedronate in the management of children with OI.
Disclosure
The authors declared no competing interests.

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Improving low bone mass in girls with adolescent idiopathic scoliosis (AIS) using calcium and vitamin D supplementation – a randomized controlled trial

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Objectives
AIS is a prevalent three-dimensional spinal deformity associated with low bone mass which has been reported to be a significant prognostic factor for curve progression in AIS. If left untreated, low bone mass in AIS could persist into adulthood thus leading to subsequent health problems. This study aimed at evaluating the therapeutic effect of oral calcium plus Vit-D supplementation for low bone mass in skeletally immature AIS girls.
Methods
This was a randomized double-blinded placebo-controlled trial recruiting AIS girls (11–14 years old, Tanner < IV) with BMD z-scores<0 and Cobb angle >15°. 330 subjects were randomly allocated to group1 (placebo), group2 (600 mg Calcium+400 IU Vit-D_3 per day) and group 3 (600 mg Calcium+800 IU Vit-D_3 per day). The study period was 2 years. At baseline (T_0) and 24-month (T_1) time-point, aBMD and BMC at bilateral femoral necks were measured with dual-energy x-ray absorptiometry (DXA); and serum 25(OH) Vit-D level with liquid chromatography tandem mass spectrometry. intention-to-treat principle was followed. ANOVA and generalized estimating equations were used for analyses.
Results
The baseline data at T0 are shown in Table 1. The corresponding mean % increases at T_1 are shown in Table 2. The gain in right and left aBMD and BMC were significantly greater in the treatment group than the placebo group (Table 2).

Table 1 Baseline data on Age, 25(OH)VitD_3 and DXA parameters

	mean±S.D. at T_0			
	Group 1 $N=110$	Group 2 $N=110$	Group 3 $N=110$	$P^{\#}$
Age	13.0±0.86	12.9±0.91	12.7±0.88	0.142
25(OH) Vit-D_3	41.4±13.3	42.3±14.3	39.4±15.4	0.306
Left BMD	0.683±0.059	0.677±0.071	0.673±0.066	0.500
Right BMD	0.694±0.064	0.681±0.068	0.677±0.065	0.126
Left BMC	1.917±0.221	1.924±0.237	1.904±0.232	0.810
Right BMC	1.960±0.254	1.940±0.244	1.928±0.217	0.601

$^{\#}P$-value from analysis using one-way ANOVA

Table 2 Percentage increase on 25(OH) Vit-D_3 and DXA parameters from T_0 to T_1 for group 1, group 2 and group 3

	Percentage increase at T_1 mean±S.D.			P^{*}		
	Group 1 N=91	Group 2 N=91	Group 3 N=88	Group 1 vs group 2	Group 1 vs group 3	Group 2 vs group 3
25(OH) Vit-D_3	22.3±47.0	62.4±65.1	97.0±88.0	<0.001	<0.001	<0.001
Left BMD	10.7±6.7	13.0±7.0	13.6±8.3	0.0237	0.0055	>0.20
Right BMD	10.3±6.7	12.8±7.0	13.4±8.3	0.029	0.020	>0.20
Left BMC	13.8±8.8	16.0±8.6	17.9±11.3	0.0421	0.0013	>0.20
Right BMC	12.5±8.5	15.5±10.0	16.8±10.4	0.0366	0.0018	>0.20

$^{*}P$-value from analysis using generalized estimating equations

Conclusion
The results provided strong evidences that treatment with 600 mg calcium+400/800 IU Vit-D_3 was effective for treating low bone mass in AIS subjects having z-score<0. Given the suboptimal 25(OH) Vit-D levels detected in this study and the association between AIS and low bone mass, Vit-D status and bone mineral density should be assessed and be followed as indicated by calcium+Vit-D supplementation for all AIS subjects.
Funding source
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Disclosure
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Effects of different socioeconomic conditions on bone mineral density in healthy Turkish female university students; relation with vitamin D status

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Objectives
Skeletal mass approximately doubles at the end of adolescence. Low areal bone mineral density (BMD) associated with vitamin D deficiency may be highly prevalent in some regions of the world. The aim of this study was to investigate effects of different socioeconomic conditions on BMD and vitamin D status in healthy Turkish female university students and to determine an association between Vitamin D status and BMD.
Participants and methods
We asked relevant questions about socioeconomic status of 138 healthy female university students in urban area. Height and weight were measured. Serum samples for vitamin D of all participants were collected in May. BMD of the lumbar spine and total body was performed by dual-energy x-ray absorptiometry (DEXA) scan (Lunar DPX series). Osteopenia was defined by a z-score below −2. Female students were grouped into three socioeconomic status as lower, middle and higher according to the educational and occupational levels of their parents.
Results
The ages of girls involved in the study ranged between 18 and 22 years, with a mean of 20.13±0.93z-scoreyears. Although vitamin D level was found to be lower in girls with lower socioeconomic status, there was no significant difference between the three different socioeconomic status ($P=0.851$). Similar results for total body and lumbar spine BMD values and z-scores were obtained ($P>0.05$). There was no significant difference regarding frequency of osteopenia among three different socioeconomic status ($P=0.164$). No significant difference was found in vitamin D levels between female with and without osteopenia ($P=0.143$). Significant positive correlations were found between total body BMD z-score and BMI and body weight ($r=0.271$ and $r=0.381$ respectively, $P<0.001$).
Conclusion
We can conclude that the differences observed in socioeconomic status do not influence the vitamin D status and BMD in female university students. This result may be explained by the fact that we live in a sunny country. Furthermore, socioeconomic differences may be decreased in urban areas. Besides, vitamin D status does not influence BMD values in young females.
Disclosure
The authors declared no competing interests.

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Osteomyelitis and septic arthritis in children: first data from the EUCLIDS network

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Background and aims
Bone and joint infections like osteomyelitis and septic arthritis occur in ~3–12/100.000 children per year in high-income countries with predominance in males. The most common causative pathogen is *Staphylococcus aureus*, however, only in 50% pathogen detection succeeds. The aim of this study is to describe clinical characteristics of osteomyelitis and septic arthritis in children recruited within the EUCLIDS network (www.euclids-project.eu).
Methods
Data was collected within the European Childhood Life-threatening Infectious Disease Study, an international and interdisciplinary network with the aim to study life-threatening bacterial infections. 195 participating hospitals from 9 countries collected data from children aged between 1 month and 18 years.
Results:
296 pro- and retrospective cases of bone and joint infections were recruited within the network between July 2012 and December 2014 (131 in UK, 46 in Austria, 39 in Switzerland, 38 in the Netherlands, 23 in Spain, and 19 in Gambia). 163 children had osteomyelitis, 104 had septic arthritis and 29 had both osteomyelitis and septic arthritis. Median age was 6 years (IQR 8.5 years), 57% children were male. In osteomyelitis most commonly the femur (30%) and tibia (27%) were affected whereas in septic arthritis it was the hip (35%) and knee (33%). The most common pathogen detected was *Staphylococcus aureus* (38%), however, in 39% of all cases no organism was identified.
Conclusion
The clinical characteristics of osteomyelitis and septic arthritis are still unchanged whereby in more than one third of our sample no causative organism was identified.
Disclosure
The authors declared no competing interests.

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Bone health among boys with Duchenne muscular dystrophy before initiation of glucocorticoids

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Background
Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy in children and it is well known for its progressive deteriorating course. Nowadays, use of glucocorticoids is the gold standard of treatment for this group of patients as it can significantly prolong ambulation, decrease risk of scoliosis, and pulmonary functions. However, the use of glucocorticoid is associated with increased risk of vertebral and lower limb fractures, which could further accelerate the loss of ambulatory capacity.
Objectives
To assess the bone health of DMD boys before initiation of glucocorticoid treatment, by studying their bone mineral density with dual-energy x-ray absorptiometry (DXA) scan, and checking the 25-hydroxy vitamin D level and past history of fractures in a single center.
Methods
Information was gathered through retrospective medical chart review for the DMD patients that have been actively followed up between the periods from January 2009 to January 2015 in our department.
Results
Results from 18 DMD boys (mean age: 6.2 years, age range: 3–10.9 years) were evaluated. None of them had any history of long bone fracture. 14 were walking well independently, three were at the late ambulatory state and one was non-ambulatory. 14 of these patients had bone mineral density assessment and their mean z-score was -1.5 (range: -3.9–1). Five patients (36%) had low bone mineral density for age with z-score < -2. Vitamin D status was assessed in 16 patients and 13 of them (81%) were found to have vitamin D insufficiency with 25-hydroxy vitamin D level less than 50 nmol/l (mean: 40.5 nmol/l, range: 20–58 nmol/l).
Conclusion
Vitamin D insufficiency and low bone mineral density are common among DMD boys even before initiation of glucocorticoids. The use of long-term steroid will further increase bone loss in this already-at-risk group. More effective forms of bone protective strategy, including bisphosphonates prophylaxis, should be considered among this group of patients.
Disclosure
The authors declared no competing interests.

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Dysosteosclerosis from a unique mutation in SLC29A3

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Dysosteosclerosis (DSS) is the rare osteopetrosis (OPT) distinguished by metaphyseal osteosclerosis with relative radiolucency of widened diaphyses and platyspondyly. In 2012, mutations in the SLC29A3 gene were discovered to cause DSS.
Here, we report a new case of DSS presenting with severe anemia and having a unique homozygous mutation in *SLC29A3*.
Our patient was the 3rd child of consanguineous Turkish parents. She presented with severe anemia (Hb 3 mg/dl) at age 4 months, and was transfused with a presumptive diagnosis of OPT. After 1 year-of-age, no hematologic abnormality was detected.
Her first fracture occurred at about 2 years-of-age. She underwent surgery several times for bilateral femoral fractures (seven fractures). BMD-DXA L2–L4 z-score was $+6$ and $+8$ at 10 and 17 years-of-ages respectively. Mineral homeostasis was intact.
She had no other systemic problems, with normal mentation and good scores in school.
She presented to us at 17 years-of-age. Height was 145.1 cm ($<3\%$), arm span was 159 cm, and upper-lower segment ratio was 0.93. Despite her past femoral fractures, she had a short upper segment and broad shoulders, but no further obvious dysmorphic features except mild prognathism, short philtrum, prominent nose, and small maxillary lateral incisors.
DSS was suspected from reviewing her radiographs taken in early childhood due to her marked metaphyseal sclerosis. Later radiographs showed more diffuse osteosclerosis with 'sandwich' vertebrae and platyspondyly.
Sequencing of all the coding exons of *SLC29A3* for the proband revealed a novel homozygous 18-bp duplication in exon-3 (c.303_320dup, p.102_107dupYFESYL) resulting in a tandem duplication of 6-amino acids. Both parents were heterozygous for this mutation.

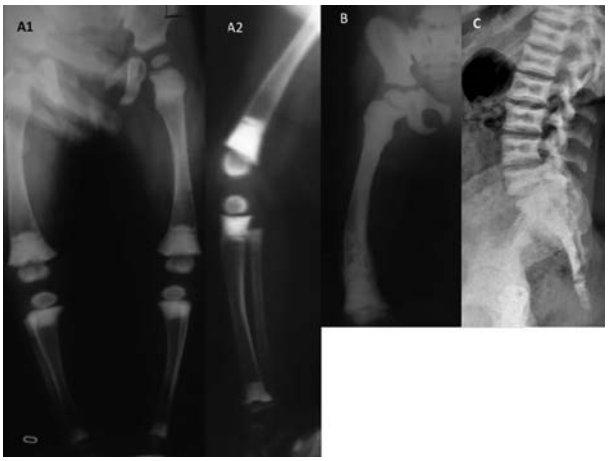

Figure 1 A. Radiographs in early childhood show metaphyseal and epiphyseal sclerosis. B. At age 6 years there is diffuse osteosclerosis and flaring in the metaphyses and metadiaphyses, cortical thinning and bowing. C. At age 17 years there is platyspondyly with sandwich vertebrae.

Conclusion
Radiographic findings in DSS evolve during growth and can be misdiagnosed when there is diffuse osteosclerosis as malignant ('infantile') OPT.
Disclosure
The authors declared no competing interests.
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Clinical predictors of low bone mineral density in children with juvenile idiopathic arthritis

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Objectives
Juvenile idiopathic arthritis (JIA) – is a chronic inflammatory disease of joints which can affect optimal linear growth, risk of fractures and bone quality during the childhood and adult life. The aim of our study was to detect the simple clinical and laboratorial markers which can predict the realization of low bone mineral density (LBMD < -2 S.D.) in children with JIA.
Methods
198 children (82 boys and 116 girls) with JIA were included in our study. For assessment of JIA activity we used onset age, duration of morning stiffness, number of active joints, white blood cells (WBC) count, Westergren erythrocyte sedimentation rate (ESR), C-reactive protein. Physician global assessment (PGA) of disease activity, measured on a 10-cm visual analog scale (VAS) where 0 = no activity and 10 = maximum activity; parent/patient global assessment of well-being, measured on a 10-cm VAS where 0 = very well and 10 = very poor. We utilized combined indexes for assessment disease activity – DAS28, JADAS71, CDAI.
Bone mineral density (BMD) was measured by lumbar spine (L1–L4) DXA with pediatric reference database. Osteocalcin, CTX, parathyroid hormone, total and ionized calcium, inorganic phosphate, total alkaline phosphatase activity was utilized for assessment of bone metabolism.
Results
Low weight and linear growth (<10 and 25%), BMI <16.6, MD VAS >5.0, DAS >2.9, DAS28 >4.2, JADAS 10 >15.6, JADAS 27 >15.1, CDAI >18.1, Steinbrocker's functional class >2, systemic arthritis, corticosteroid treatment, arthritis duration >4.5 years, number of active joints >5, number of painful joints >9, morning stiffness >90 min, parental overall JIA activity (VAS) >5.8, ESR >16 mm/h, CRP >22.6 mg/l increased the risk of LBMD in JIA children. Among metabolic markers Ca total ≤ 2.42 mmol/l and Pi >1.59 mmol/l also increased the possibility of LBMD.
Conclusion
Our data can help in identification the group of risk of JIA patients with LBMD and suggest the indications for densitometry evaluation of JIA children.
Disclosure
The authors declared no competing interests.
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The role of vitamin D in growth physiology in early-aged and preschool children

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Objectives
The linear growth of child is characterized by the presence of phases of growth spurt which allowed to rich the peak growth to the end of puberty. Acceleration of velocity of linear growth required the adequate calcium and vitamin D supplementation necessary for mineralization of bone matrix and osteoblast proliferation.
The aim of our study was to evaluate changes of serum concentrations of vitamin D during the growth phases.
Methods
75 healthy children aged 1–7 years were enrolled in our study. The weight and linear growth was evaluated according to regional standards (Moscow, 2005). 25-OHD_3 levels were measured by immunoassay method.
Results
Low birth weight and/or linear growth was revealed in 37% children, rickets was diagnosed in 37% and 19% had disharmonious physical development. Every third child had bile ducts dyskinesia. The lowest vitamin D level in early-aged children was detected whom lived in orphanages or in families with low income (6.57 ± 7.29 ng/ml). The vitamin D level in children from low income families ranged from 17.1 ± 4.26 to 24.45 ± 1.73 ng/ml.
The vitamin D (25-OHD_3) level in whole group children aged 1–6 years ranged from 2.72 to 58.87 ng/ml. The lower vitamin D levels were in children with different bile duct dysfunction. The prevalence of children who had vitamin D (25-OHD_3) levels <20 ng/ml was 26.8%.
In the group of children in the age of 4 years we have found transient increase of serum vitamin D levels, accompanied with decrease osteocalcin and C-terminal telopeptides levels. These findings could interfere physiological mechanisms of preparation of children's skeleton to growth spurt.
Conclusion
Changes of age-related levels of vitamin D (25-OHD_3) in children 1–6 years allowed to think about the role of vitamin D in growth physiology.
Disclosure
The authors declared no competing interests.
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Secondary osteoporosis in boys with Alagille syndrome – case report

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Alagille syndrome is a multiorganic disorder, which particularly manifests itself with cholestasis, characteristic facial features, circulatory systems defects, defects of the front segment of the eye, dysplastic changes in bones and kidneys and impaired angiogenesis. The disease is caused by Jagged 1 gene mutation (JAG, 20p12 chromosome) which encodes ligand for Notch receptor. JAG/ Notch signaling pathway plays important evolutionary role in cell differentiation in organogenesis process. JAG expression in numerous tissues leads to multiorganic manifestation. Jag expression is substantially important for skeleton growth and bone cells activity. Its malfunction may lead to spine and long bones abnormalities, neoplastic changes and osteoporosis.
A 10-years-old boy with Alagille's syndrome was diagnosed with secondary osteoporosis. The diagnosis was based upon clinical symptoms (9 bone fractures and crus pains) and densitometric examination (DXA – dual x-ray absorptiometry) method in pediatric program (TBLH z-score -3.2). Treatment included vitamin D and calcium supplementation. However, significant improvement was observed after liver transplant (advised primary disease treatment). Currently z-score TBLH reached -1.5. For over 2 years, no bone fractures or aforementioned pains have been observed.

Conclusion
The basis of secondary osteoporosis treatment is the primary disease treatment. Furthermore, densitometric examination is necessary both in diagnostics and skeletal condition monitoring.
Disclosure
The authors declared no competing interests.
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X-linked spinal muscular atrophy caused by de novo c.1731C>T substitution in the UBA1 gene

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Infantile spinal muscular atrophy X-linked 2 (SMAX2) is a rare form of spinal muscular atrophy manifesting in severe hypotonia, areflexia, arthrogryposis, facial weakness and cryptorchidism, as frequently accompanied by bone fractures.
We present a boy patient with SMAX2 who presented typical symptoms from birth, as preceded by reduced fetal movements in the second and third trimester of pregnancy. In the first days of life the patient was found to have suffered fractures of the right femur and right humerus. Clinical examination revealed a myopathic face with characteristic tent-shape open mouth, tongue fibrillations, profound muscle weakness, areflexia, multiple contractures, cryptorchidism and mild skeletal abnormalities. Due to observed bone fractures, bone mineral density was estimated using dual x-ray absorptiometry (DXA) method in Infant program, which bore a result of BMD TBLH 0.273 g/cm^2. Molecular analysis revealed *de novo* c.1731C>T substitution in the *UBA1* gene.
It is concluded that the diagnostic clinical criteria of SMAX2 should be expanded by a history of decreased fetal movement and the presence of skeletal abnormalities. Exon 15 of *UBA1* is a specific hot spot for mutations.
Disclosure
The authors declared no competing interests.
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Bone robusticity in two distinct skeletal dysplasias: an evaluation of the second metacarpal, a surrogate for bone strength

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Radiographs of the second metacarpal are used to assess bone strength development in paediatric populations. Children with achondroplasia and osteogenesis imperfecta (OI) have known differences in bone strength. Details of how bone strength develops and compares within these populations to unaffected children are lacking. A data set for patients with achondroplasia and OI was established.
A retrospective IRB-approved review of bone-age films ($n=67$; 1–11 films/patient) from patients (5 months–16 years+3 months old) with achondroplasia (six males; ten females) or OI (nine males; 11 females) was conducted. A sample of modern controls (diagnosis: leg-length discrepancy) matched historical measurements from the Bolton-Brush collection (6 months–16 years). Metacarpal length (Le) was measured from the proximal end to the most distal ossified end along the midshaft axis. Outer and inner diameters were measured at 50% and 60% of the length, averaged, and used to calculate total cross-sectional area (Tt.Ar) and cortical area (Ct.Ar) using a circular approximation. To adjust for differences in body size, we compared robustness (Tt.Ar/Le) and relative cortical area (RCA=Ct.Ar/Tt.Ar) among groups.
Achondroplasia patients tend to have both robusticity and RCA values above the most robust Bolton-Brush tertile (Figure 1A). This robust phenotype was consistent with the reduced longitudinal growth seen in achondroplasia patients. Increased RCA values were unexpected and may indicate deregulated mass-accumulation. In contrast, OI patients followed the Bolton-Brush pattern of decreased robusticity and increased RCA, but not the distribution. OI patients all fell in the most slender tertile (Figure 1B). No sexual dimorphism was noted in this study (Figure 1C).

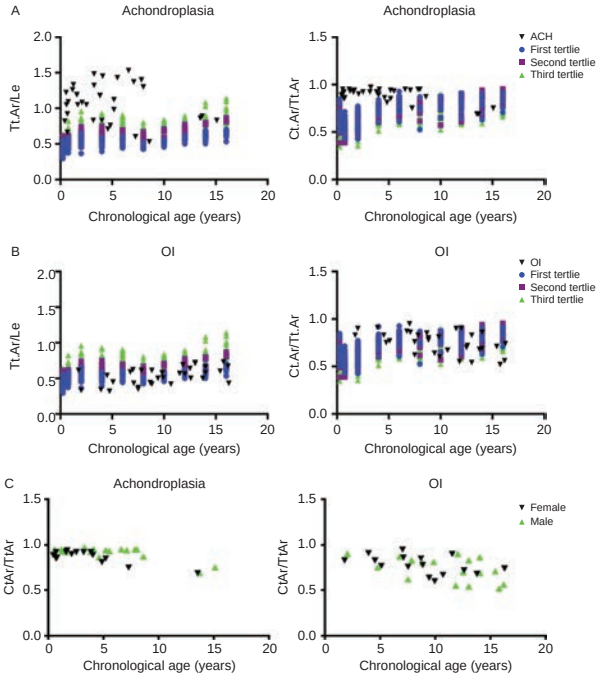

Figure 1

The lack of sexual dimorphism in the dysplasia populations is in contrast to that reported in the unaffected population. We suggest that the underlying dysplasia overrides the sex-specific effects on bone strength development. The contribution of the specific mutation is unknown and needs to be further studied.
Disclosure
Dr. Raggio sits on the Medical Board of the Osteogenesis Imperfecta Foundation.
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P103

Gait assessment in children with childhood hypophosphatasia: impairments in muscle strength and physical function

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Objectives
Hypophosphatasia (HPP) is the rare inherited metabolic disease caused by low tissue nonspecific alkaline phosphatase activity. HPP manifests a wide spectrum of complications, which may include HPP-related rickets and compromised physical function in children.
Methods
We report on clinical gait assessments based on archival video recordings of six children with onset of HPP symptoms at ≧6 months and documented HPP-related skeletal abnormalities enrolled in a retrospective non-interventional natural history study. Children with ≧2 clinical videos of basic mobility available between ages 5–15 years were eligible for inclusion in this sub-study. Gait

performance was assessed using a version of the 12-point performance-oriented mobility assessment[1] modified to provide improved sensitivity for HPP-related impairments (MPOMA-G; 12 = no impairment; 0 = greatest impairment). A physical therapy descriptor checklist and chart review provided additional information on physical function. Data are reported as median (min, max).

Results

All six participants were boys from one study center; five had bowing of the long bones and all had gait disturbances. Age at first assessment (FA) and last assessment (LA) was 6.2 years (5.3, 10.7) and 11.1 years (8.2, 14.9) respectively. At FA, total MPOMA-G score was 6.0 (3.0, 11.0); all patients had trunk sway or compensatory patterns in the trunk or arms; five a steppage gait pattern, and four reduced step size and continuity. At LA, MPOMA-G was 7.5 (4.0, 11.0; change from FA: +1.5 (0.0, +2.0); $P = 0.0625$) with no consistent pattern of change in any MPOMA-G component. At LA, four patients were unable to achieve a period-of-flight during running; all required self-support with a hand to transition from the floor to standing. Time standing on one foot (when data available) ranged from 1.5 to 5.6 sec, less than healthy peers.[2] Overall, proximal muscle weakness (deficits in hip muscle strength, positive Trendelenburg sign) was common.

Conclusions

These data demonstrate that children with HPP can have clinically significant and persistent gait impairments indicative of reduced balance and muscle strength. The burden of disease in such children compromises their community participation and activities of daily living.

Disclosure

Dawn Phillips received consulting fees from Alexion Pharmaceuticals, Inc. Marc Vallee, Kenji P Fujita are the employees of Alexion Pharmaceuticals, Inc. Katherine L. Madson has received honoraria from Alexion Pharmaceuticals, Inc. Michael P. Whyte has received honoraria, research grants, and travel support from Alexion Pharmaceuticals, Inc.

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References

1. Tinetti ME. *Am J Med.* 1986.
2. Folio MR, Fewell RR. *Pro-Ed* 2000.

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P104

Effect of intravenous pamidronate in the treatment of skin calcinosis in the course of juvenile dermatomyositis – a story half-told

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Juvenile dermatomyositis (JDM) is a severe connective-tissue disease of unknown etiology characterized by inflammatory process affecting muscles and skin, with subsequent presentation in the joints, esophagus, lungs, and the cardiovascular system. Clinical presentation also includes deposition of calcium in the skin (*calcinosis cutis*) which is typically seen in the juvenile DM, contrary to the adult form. The pathogenesis of JDM-related calcinosis remains unclear whereas it is a complication developed by 30–70% of patients, and is a major cause of morbidity and impaired quality of life.

We present a case series of skin calcinosis in three patients (13-year-old boy, 13-year-old girl and a 6-year-old girl) diagnosed of JDM. The aim of this study was to depict clinical course of cutaneous calcifications, and to demonstrate the effects of treatment with cyclic intravenous pamidronate (PAM). The children met the standard diagnostic criteria for JDM and all were intensively treated with glucocorticoids, methotrexate and/or immunoglobulins for more than 2 years. Massive formations of calcium deposits in different locations of the skin and soft tissues were observed while in one of these patients, calcinosis was the first symptom predating the clinically apparent JDM. Some of the foci reached a large size, tumor-like shape and considerably limited joint mobility. Over the time of observation, the children received two to eight pamidronate series (3-day-long cyclic iv. PAM administration, 4-months intervals). A distinct alleviation and reduction of size of the deposits were observed during the treatment. No newly formed deposits were found whereas most of the foci disappeared, and physical function had improved; no severe adverse effects were reported except of mild transient hypocalcemia in one patient.

Conclusion

The PAM therapy is an effective and safe symptomatic management of the calcinosis in the course of JDM, although the cause-effect mechanism remains not fully clear. A question arises: What is the optimal treatment for calcinosis in the course of JDM, when the treatment should be implemented and for how long should it be continued? There is a need of further investigation regarding the optimal dose and maintenance therapy for disseminated skin calcinosis and/or combination with other drugs being possibly more effective.

Disclosure

The authors declared no competing interests.

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P105

Refractory hypercalcaemia of malignancy: responsiveness to Denosumab and Zoledronate

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Background

Hypercalcaemia secondary to malignancy is rare in children and adolescents. Parathyroid hormone related peptide (PTH-rP) secreted by malignant cells increases bone resorption and renal calcium retention causing hypercalcaemia. We report two cases of hypercalcaemia of malignancy refractory to treatment with pamidronate and corticosteroids but responsive to treatment with Denosumab and Zoledronic acid.

Case 1

Presenting problem: A 17-year-old boy with epidermolysis bullosa presented with advanced squamous cell carcinoma of the left leg and symptomatic hypercalcaemia (serum adjusted calcium, 4.2 mmol/l). PTH was suppressed at 0.7 pmol/l. Serum 25 hydroxy vitamin D level was 31 nmol/l (normal range >50 nmol/l). PTH-rP and 1, 25 dihydroxy vitamin D levels were elevated at 2.1 pmol/l (0.0–1.8) and 173 pmol/l (43–143) respectively.

Management: The hypercalcaemia was initially managed with hyperhydration, prednisolone and intravenous pamidronate (1 mg/kg/dose × 2 doses), following which only transient improvement was noted. Despite further aggressive management with these treatment options, serum calcium remained persistently elevated at 3.39 mmol/l. As he was symptomatic, a trial dose of subcutaneous Denosumab (60 mg) was given, following which the calcium fell to 2.86 mmol/l within 24 h and normocalcemia was sustained a week later.

Case 2

Presenting Problem: A 17-year-old girl with pelvic rhabdomyosarcoma was hypercalcemic (serum adjusted calcium, 3.19 mmol/l) with supressed PTH of 0.3 pmol/l and serum phosphate of 2.2 mmol/l. Serum 25 hydroxy Vitamin D was 28 nmol/l and renal profile was normal.

Management: The initial treatment comprised hyperhydration, furosemide, prednisolone and intravenous pamidronate, after which serum calcium remained persistently elevated at 4.04 mmol/l. At this point intravenous Zoledronic acid (2 mg) was administered, following which the serum calcium dropped to 2.79 mmol/l within 24 h and normocalcaemia was sustained for several weeks, with no adverse effects.

Discussion

Denosumab is a monoclonal antibody which neutralises RANKL (receptor activator of nuclear factor k-B ligand), inhibiting the function of osteoclasts thereby preventing generalized bone resorption. Zoledronic acid blocks osteoclast resorption and has a more potent calcium-lowering effect than pamidronate. These two drugs widen the treatment options for patients with resistant hypercalcaemia of malignancy.

Disclosure

The authors declared no competing interests.

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P106

Metatropic dysplasia is associated with increased fracture risk and increased markers of bone turnover

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Metatropic dysplasia (MD) was first described by Maroteaux *et al.* in 1966. Its name was derived from the Greek word *metatropos* which means 'changing pattern' because individuals with this diagnosis begin life with a short-limbed dysplasia and a long trunk with narrow chest, and over time their dysplasia becomes short-trunked due to progressive kyphoscoliosis[1]. It is now recognized that MD is caused by gain-of-function mutations in transient receptor potential vanilloid 4 (TRPV4) and belongs to a family of dysplasias which includes: spondylometaphyseal dysplasia, Kozlowski type (SMDK), and brachyolmia[2]. TRPV4 is a non-selective cation channel, important in the regulation of intracellular calcium. It is widely expressed in human nervous, urinary, respiratory, and musculoskeletal systems[3]. In our clinic, it became apparent over time that there was a higher than expected fracture frequency in MD. To explore further we designed an Institutional Review Board approved protocol for a detailed retrospective review of this patient population. Of the 20 patients evaluated at our institution in last 9 years with MD or SMDK, there were ten males and ten females. 8/20 (40%) of patients had at least one fracture, and 5/20 (25%) of patients had two or more fractures. Evidence of increased bone turnover, with elevated TRAP, NTX and osteocalcin levels were noted. When TRPR4 is over-expressed in osteoclasts in transgenic mice, increased osteoclastic numbers and increased resorption activity were noted. This resulted in bone loss and decreased bone mass in these mice[4]. Taken together with our observations, it suggests that MD is not only a disorder of the growth plate leading to dwarfism, but also a disorder of bone leading to osteopenia and fracture.

References
1. Boden SD. *et al.* Metatropic dwarfism. *J Bone Joint Surg Am.* 1987. **69**(2): 174–84.
2. Krakow D. *et al.* Mutations in the Gene Encoding TRPV4 Produce Spondylometaphyseal Dysplasia, Kozlowski Type and MD. *Am J Hum Gen.* 2009. **84**(3):307–315.
3. Everaets *et al.* TRPV4: from structure to disease. *Prog Biophys Mol Biol.* 2010. **103**(1):2–17.
4. Masuyama R. *et al.* Calcium/calmodulin-signaling supports TRPV4 activation in osteoclasts and regulates bone mass. *J Bone Miner Res.* 2012.**27**(8):1708–21.

Disclosure
The authors declared no competing interests.

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P107

Bone mineral density in Pelizaeus Merzbacher disease

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Objective
To examine the bone mineral density (BMD), fracture occurrence and history in a cross-section of subjects with Pelizaeus Merzbacher Disease (PMD).
To describe the effect of pamidronate therapy on BMD over time in treated PMD patients.
Methods
We examined the medical history, medications, level of ambulation, fracture history and DXA results in 15 boys with PMD. Body sites scanned included whole body (WB) when possible, lumbar spine (LS), and lateral distal femur (LDF). Age and gender-matched *z*-scores were calculated using manufacturer-provided normative values for LS and WB, and published norms for the LDF.
Results
15 males with a mean age of 14.2 years (range 1.1–33.2) at the time of initial DXA were included in this study. All were non-ambulatory. Three subjects reported non-traumatic fracture. This subgroup received bisphosphonate according to a serial cyclic protocol. Standard pediatric DXA sites were problematic; WB measure was only able to be obtained on eight subjects. LS was obtained on nine subjects and six subjects had spinal fusion rods. We were able to obtain LDF DXAs on every subject. BMD *z*-scores were not available for the two youngest subjects.
BMD was low at all sites measured in all subjects. Mean (and range) total body less head BMD *z*-score was −3.7 (−2.7 to −6.2). Mean LS BMD *z*-score was −4.1 (−2.0 to −6.5); for the LDF: R1 −4.6 (−2.6 to −7.4); R2: −8.9 (−2.7 to −25.1); R3: −4.6 (−2.1 to −7.9).
The three subjects treated with pamidronate had no adverse effects to the cyclic protocol. Two had serial DXA scans with 2 and 3.5 years of observation. BMD improved and *z*-scores improved in all LDF regions with treatment and no additional fractures occurred.
Conclusions
Boys with PMD have low BMD at all body sites tested, particularly in the lower extremities. In a subgroup with non-traumatic fractures, LDF BMD improved with bisphosphonate and no additional fractures have occurred. As demonstrated in other populations with physical disabilities, the LDF proved to be an easily-obtained, useful alternative DXA site.
Disclosure
The authors declared no competing interests.

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P108

Unique occurrence of long bone fragility with cranial hyperostosis: Searching for the genetic culprit

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Background
Systemic alterations in Runx2 expression have been shown to affect flat and long bone formation differently: Inactivating mutations cause low-turnover bone disease and patent fontanels in cleidocranial dysplasia, while overexpressing mutations cause metaphyseal dysplasia with maxillary hypoplasia and brachydactyly. The two conditions have inverse skeletal phenotypes. We know of no descriptions of these disorders in a patient without duplications or mutations of Runx2.
Presenting problem
The 5-year-old son of non-consanguineous Austrian parents presented with a unique combination of long bone fractures due to bone fragility and severe scoliosis with cranial hyperostosis and craniosynostosis. An iliac crest biopsy showed an extreme decrease in cancellous bone matrix mineralization and an increase in bone turnover, in line with elevated serum ALP and TRAP5b. To date, his linear growth and psychomotoric development are unaffected, but his fracture rate is high (2× right femur, 6× left femur, 5× left tibia, 1× right tibia, 1 sacrum).
Clinical management
Bisphosphonate treatment was withheld until his neuroforaminal width stabilized. Calvarial vault remodeling was necessary due to symptomatic craniosynostosis. Telescopic rods were implanted in both femura because of repeated fractures and bowing.
Genetic analysis
Direct gene sequencing for several possible genetic causes (RUNX2, TNFRSF11B, SOST, LRP5, SERPINF1, FGFR1-3, TWIST1) detected no relevant mutations. SNP microarrays and whole exome sequencing have revealed no underlying alterations so far.
Discussion
We have not been able to identify any underlying genetic cause for our patient's complex phenotype. Many of his clinical features resemble metaphyseal dysplasia with maxillary hypoplasia and brachydactyly caused by duplications of Runx2 which have been excluded in this patient. We speculate that genetic alterations of a novel key regulator of ossification associated with Runx2 could have caused this uncommon clinical picture.
Disclosure
The authors declared no competing interests.

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P109

Effects of inorganic phosphate and FGF23 on C2C12 myoblast cells

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Objectives
Dysregulation of systemic phosphate homeostasis is often associated with impairment of musculoskeletal tissue function. Many factors such as calcium

levels and dysegulated endocrine mechanisms are thought to contribute. Inorganic phosphate and FGF23 have been shown to act *via* similar signaling pathways in several cell types but we are not aware of any detailed investigations into their effect on the differentiation and viability of skeletal muscle cells. We therefore investigated their effect on skeletal muscle cells in a murine *in vitro* model.
Methods
C2C12 muscle progenitor cells were differentiated under single and combined treatments with inorganic phosphate and/or FGF23 and Klotho. Expression of differentiation markers (myogenin, MyHC, MyoD, Myf5) were analyzed by RT-PCR. Proliferation rate was analyzed by measurement of BrdU incorporation. Metabolic activity was examined by EZ4U assays.
Results
Phosphate treatments inhibited the expression of differentiation markers in C2C12 cells in a dose-dependent manner. The altered expression profile was associated with increased proliferation rates and metabolic activity. FGF23/ Klotho treatments did not alter gene expression of C2C12 cells or change the effects observed under phosphate treatment.
Conclusion
High phosphate loads directly inhibited muscle cell differentiation in a C2C12 model system. FGF23/ Klotho treatments did not influence these effects. Knowledge of the distinct effects of phosphate could help us to optimize treatment of hyperphosphatemia and aid to prevent musculoskeletal diseases.
Disclosure
The authors declared no competing interests.
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P110

Abstract withdrawn.

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P111

Is groupwork an effective way to improve transition for young people with osteogenesis imperfecta? A pilot study
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Objectives
Within the National Health Service there is a recognised need for supporting young peoples transition into adult services[1]. Focus groups and forums have historically been used to identify how to achieve 'good' transition between services, from the perspective of patients, carers and professionals. A recent article recommended an individualised programme supporting transition for young people with osteogenesis imperfecta (OI)[2]. The aim of our project was to evaluate whether groupwork was enjoyed by young people with OI, if their understanding of transition increased from this and how their healthcare team can support them during the transition process.
Method
44 adolescents with OI aged 10–17 years were invited to a transition group, 13 attended. Of the participants nine had mild OI, three moderate and one severe (four participants use wheelchairs the majority of the time). Topics covered included an introduction to transition, the roles of the OI health care professionals and how transition plans can support a move to adult services. Anonymised pre and post questionnaires were used to explore their perspectives and effectiveness of the transition group.
Results

- 11 pre and post questionnaires were completed.
- Ten participants reported to have enjoyed the group and would recommend it to other young people with OI.
- Nine participants reported to have increased confidence when talking about issues relating to transition.
- There was an 18% increase in the proportion of participants understanding how different healthcare professionals can support them through transition.
- Two emerging themes were identified 'not feeling alone' and 'change in hospital care'.

Conclusion:
Overall groupwork was found to be an effective way of supporting young people in their understanding of transition. Due to the relatively small number of attendees' (30% of those invited) an alternative data collection method, such as semi-structured interviews or a focus group, would have provided more detailed feedback. It would be interesting to explore the reasons why the remaining 31 young people chose not to attend, even when given two opportunities. This pilot study supports the need for groupwork when focusing on transition, however further evaluation is needed to explore its on-going effectiveness.
References
1. Care Quality Commission. From the Pond into the Sea: Children's transition into adult health services. 2014.
2. Maman JD. Frank R. Trudy W. Joanne R. Francis HG. and Christophe B. From pediatric to adult care: strategic evaluation of a transition program for patients with osteogenesis imperfecta. *BMC Health Services Research*, 2014 **14**:489.
Disclosure
The authors declared no competing interests.
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P112

Type V osteogenesis imperfecta: confirmation of highly characteristic radiographic findings in early infancy
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Type V OI is characterised by interosseous membrane calcification and hyperplastic callus formation, but the infantile phenotype is less well recognised. In 2012 Arundel *et al.* described distinctive radiographic changes in an infant with type V OI. We report two further male infants (with genetic confirmation of type V OI) confirming the highly characteristic and consistent radiographic appearances that should aid early diagnosis.
Case 1 – Presented with respiratory distress at 4 weeks of age having had stridor since birth. He underwent aryepiglottoplasty aged 5 weeks. A post-operative radiograph showed a rib fracture. At 5 months, discomfort on handling led to identification of a vertebral fracture and commencement of pamidronate.
Case 2 – Presented at 6 weeks of age with multiple rib fractures. Pamidronate was started at 3–4 months of age, by which time he had sustained another rib fracture despite careful handling.
Skeletal surveys (taken at 6 and 7 weeks of life respectively) in each case revealed common radiographic appearances: flaring of metaphyses of long bones with sclerotic and irregular margins; gracile ribs; and triangular-shaped radiodensities of the anterior margins of the vertebral bodies. There was maintenance of vertebral body height initially. In both cases 25OH vitamin D concentrations were normal (57.7 and 52.4 nmol/l). Both cases were heterozygous for the c.-14C>T *IFITM5* mutation confirming type V OI.
Both cases had near-identical radiographic appearances in early infancy, which are in keeping with those in the published case, as is the early development of vertebral crush fractures in case 1. In one centre, 6/7 consecutive cases of type V OI (not including either case above) had radiographic confirmation of multiple vertebral fractures by 18 months (median 13.5 m; range 7–17 m); 1/7 was initially managed overseas and the earliest confirmation of vertebral fractures was 32 months.
Early recognition of the type V OI phenotype helps remove uncertainty and target genetic testing; advice can be given to minimise the risks of hyperplastic callus; and consideration can be given to earlier intervention (bisphosphonate treatment; handling and seating advice) to minimise the vertebral deformity that commonly develops in the first year of life.
Disclosure
The authors declared no competing interests.
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P113

Comparison of cost benefits and efficacy of Zoledronic acid and Pamidronate in the treatment of osteogenesis imperfecta in children
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Intravenous (IV) Pamidronate (PAM) has been used in the treatment of Osteogenesis Imperfecta (OI) and is known to increase bone mineral density

(BMD) and reduce the incidence of fractures. However an attractive alternative is the more potent IV Zoledronic acid (ZOL).
Objectives
To determine the clinical efficacy of IV PAM vs ZOL in children with mild to moderate OI and compare the cost benefits of the two drugs.
Methods
A retrospective review of patients aged ⩾5 years with type I or IV OI, who started either PAM or ZOL (2001–2014) at a tertiary centre was conducted. PAM was administered in cycles of 1.5 mg/kg per day over 2 days every 3 months and ZOL as a single dose of 0.05 mg/kg 6 monthly. Lumbar Spine (LS) DXA was performed pre and 1 year post treatment. Cost analysis was performed for a 5 years period based on drug cost, nursing and medical time, equipment and days in hospital per year (8 vs 2 days per year, for PAM vs ZOL).
Results
A total of 40 patients were identified, 20 in each group. LS BMAD z-scores increased significantly in both groups ($P<0.001$). The median (interquartile range) increase in LS BMAD z-score for the PAM group (1.67 (1.46–2.21)) and the ZOL group (1.75 (1.46–2.00)) was not significantly different. Total cost per treatment cycle per patient was £498 for ZOL and £1157 for PAM. Annual costs for bisphosphonate therapy (BP) decreased since introduction of ZOL (see Figure 1).

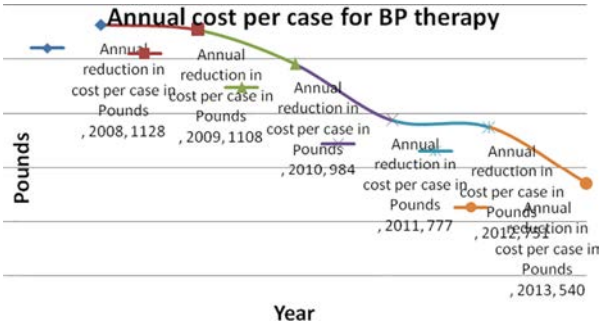

Figure 1

Conclusion
ZOL is a significantly cheaper alternative to PAM with comparable efficacy, resulting in substantial annual savings for health care providers. ZOL is also a more convenient option for patients due to fewer hospital visits.
Disclosure
The authors declared no competing interests.
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P114

Influence of pubertal development and body composition on bone mass accrual in apparently healthy school children aged 6-17 years

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Objectives
To evaluate progression of BMD and bone mineral content (BMC) during pubertal development and Influence of body composition and vitamin D on BMD and BMC in children and adolescents.
Material and method
This cross sectional study was part of an ongoing health survey of Delhi school children which recruited 1905 apparently healthy school children (835 boys; 1070 girls) in the age group of 6–17 years. After brief history, anthropometry and pubertal assessment, blood samples were collected for measurement of serum 25-hydroxy vitamin D (S.25Vit-D) and intact parathyroid hormone (iPTH). Whole body DXA scans were performed using GE Lunar Prodigy scanner. Areal BMD was computed. fat mass index (FMI) was calculated by total fat mass in Kg/square of height in meters.
Results
The mean age of subjects was 13.27 ± 2.48 years and mean FMI was 5.59 ± 3.1 kg/m^2 (boys – 4.65 ± 3.1; girls – 6.5 ± 2.81). Vitamin D deficiency (S.25 Vit-D <20 ng/ml) was present in 96.8% subjects. BMD and BMC increased progressively with progression of puberty in both boys and girls but maximum gain was observed from pubertal stage 2–4. In pre-pubertal children, boys had significantly higher Total BMC and BMD/BMC at spine than girls but Femur Neck (FNBMD/BMC) was not different. Boys showed higher percentage rise in BMD from stage 1–5 in comparison to girls. FMI showed significant positive correlation with TBMC; $r=0.40$, $P=<0.001$, lumber spine BMD (LSBMD); $r=0.11$, $P=<0.001$ and with FNBMD; $r=0.13$, $P=<0.001$; but did not show any significant correlation with S.25Vit-D or iPTH. Similarly, total lean mass also showed significant positive correlation with TBMC, LSBMD and FNBMD in all subjects as well in all pubertal groups. S.25 Vit-D was also positively correlated with TBMC ($r=0.13$, $P=<0.001$), LSBMD ($r=0.15$, $P=<0.001$) and FNBMD ($r=0.06$, $P=0.006$).
Conclusion
BMD progressively increases during pubertal development with maximum gain occurring between pubertal stages 2 and 4. FMI is positively correlated with BMD/BMC all three sites.
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P115

Vitamin D and bone mineral density in children with Duchenne muscular dystrophy relation to fractures and ambulation status

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Objectives
To evaluate vitamin D and bone mineral density (BMD) status in children with Duchene muscular dystrophy (DMD) in relation to fractures and ambulation status using gross motor scale function classification system (GMFCS).
Methods
Clinical data of 53 DMD patients (mean age 12.1 years, range 4.9–19.6) at the first visit to the Endocrine/Bone Clinic at Nationwide Children's Hospital were retrospectively studied. The patients were stratified to two groups according to GMFCS score of 1–3 (ambulatory) and 4–5 (non-ambulatory) and presence or absence of fractures.
Results
Vitamin D insufficiency was found in 72.7% (25OHD <30 ng/ml) or 25% (25OHD <20 ng/ml) of the patients. Overt vitamin D deficiency (25OHD <10 ng/ml) was observed in 2.2%. Thirty patients (56.6%) had fractures, 7 (23.3%) of whom had vertebral fractures. Patients with GMFCS score of 1–3 ($n=27$ or 50%, mean age 9.7 ± 2.6 years) had higher mean lumbar and total body BMD height-adjusted z-score (HtZ) than those with GMFCS 4–5 (mean age 14.5 ± 2.4 years) (lumbar HtZ -0.09 ± 1.07 vs -1.042 ± 1.5, $P=0.03$, total body HtZ -2.5 ± 2.0 vs -5.6 ± 2.5, $P=0.0002$), and also less fractures (0.6 ± 0.8 vs 1.2 ± 1.2, $P=0.046$). Mean duration of steroid treatment was longer in patients with fractures than those without fractures (5.9 ± 3.2 vs 4.1 ± 2.5 years, $P=0.03$), but was not significantly different between those with low or high GMFCS score. Height z-score was lower in those with fractures than those without ($P=0.031$). There were no correlations between 25OHD and fractures or 25OHD and BMD. There were no differences in mean 25OHD and BMD HtZ between those with and without fractures.
Conclusions
Non-ambulatory DMD patients had more fractures and worse BMD z-scores than those who were ambulatory, as expected. Factors associated with fractures were short stature, long duration of steroids, and the ambulation status, but not vitamin D and BMD z-score. Duration of steroid treatment did not correlate with ambulatory status, likely explained by early loss of ambulation following fractures of lower extremity in some patients, independent of duration of steroid use.
Disclosure
The authors declared no competing interests.
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P116

Osteopetrosis with uncommon final height: can only local IGF1 hold normal growth during pubertal spurt?

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Background
Final stature is a result of concomitant growth hormone (GH)-IGF1 axis integrity, a healthy environment and genetic background. Occasionally, growth occurs despite remarkable impairment in hormone profile. Presenting problem: An uncommon case of longitudinal growth in a boy with very low IGF1 concentrations and clinical diagnosis of osteopetrosis. Clinical management: We report on the case of a 19 year-old male patient with the diagnosis of osteopetrosis who had a falloff in growth at the age of 14 years, Tanner G1P1, but recovered height gain velocity months latter, suggesting a prepubertal slowdown in growth. However, his IGF-I concentrations were consistently low (<-2 SDS) . Three GH provocative tests were performed and resulted in appropriated cortisol release, but no response of GH to the stimulus. Lumbar spine bone mass was increased (z-score $=+5.1$) and there were calcifications within the skull base but normal brain MRI. At age of 16 years he had a femural fracture with abnormal consolidation, leading to walking limitation. His final height is 179 cm (0.43 SDS), above familial target height.
Discussion
This case report describes a patient harboring osteopetrosis, a disease usually associated with short stature and normal GH/IGF1 axis. Curiously, the patient exhibited normal height development in spite of GH deficiency. Further studies are necessary to evaluate the role of growth factors production and action on bone microenvironment in this condition. Preliminary molecular studies were performed and confirmation of the mutation and its clinical correlation are ongoing.
Disclosure
The authors declared no competing interests.

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P117

Familial hypocalciuric hypercalcemia in two Chinese families – common and uncommon features

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Background
Familial hypocalciuric hypercalcemia (FHH) is a rare autosomal dominant condition with an estimated prevalence of 1 in 78,000. The commonest cause of FHH is inactivating mutations of the calcium-sensing receptor (CASR) gene, with the rest mostly caused by missense mutations of the GNA11 and AP2S1 genes. FHH is characterized by persistent mild-to-moderate hypercalcemia, hypocalciuria with calcium-creatinine clearance ratio $\leqslant 0.01$. The disease runs a benign course. Rare complication includes pancreatitis.
Presenting problem: In the first family, the mother and the two daughters were affected. Both daughters were incidentally found to have persistent hypercalcemia, with normal to mild inappropriate elevation of parathyroid hormone (PTH). The calcium-creatinine clearance ratio of the elder sister was 0.01. The second family involved the mother and her daughter. The daughter was incidentally discovered to have hypercalcemia at birth. On retrospect, the mother had history of back pain with small renal stones found on imaging. She was confirmed to have hypercalcemia on subsequent workup. Her calcium-creatinine clearance ratio ranged from 0.005 to 0.02 (The ratio of 0.02 was documented during pregnancy, with an absolute daily calcium excretion of 9.3 mmol per day). The PTH pattern was similar to the first family, but both mother and baby also had concomitant vitamin D deficiency. Both families were genetically confirmed to have FHH.
Clinical management
The diagnosis of FHH hinges on a low calcium-creatinine clearance ratio. Collection of 24-h urine for calculating the ratio is difficult for infants, therefore, to start testing the parent with hypercalcemia, and follow with mutation analysis might be a more practical strategy.
Both mother and baby of the 2nd family responded to vitamin D supplement without exacerbation of the hypercalcemic state.
Discussion
The first family showed typical features of FHH. For the second family, the incidental finding of nephrolithiasis in the mother highlighted the fact that we should be open-minded for the diagnosis of FHH in hypercalcemic patient despite the atypical presentation of nephrolithiasis. Moreover, Vitamin D deficiency, though uncommon, had been well reported in patients with FHH and should be tested as part of the workup for FHH and treated accordingly.
Disclosure
The authors declared no competing interests.

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P118

Changes in total body and regional bone mass in relation to body composition in children with osteogenesis imperfecta treated with pamidronate

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Background
In patients with osteogenesis imperfecta (OI), a rise in age-specific total body and regional bone mass is well recognised. In contrast changes in body size-adjusted bone mass in relation to changes in body composition following pamidronate therapy remain relatively unexplored.
Methods
Changes in total and regional bone mass in relation to body composition in children with OI receiving pamidronate (3 mg/kg per day over 3 days, 3 monthly) were analysed over 2 years. Subtotal body (TBLH) and lumbar spine bone mineral content (LSBMC-grams), bone area (LSBA–cm^2), areal bone mineral density (LSaBMD–g/cm^2), total body fat mass (grams) and lean mass (grams) were estimated by DXA in 26 children over 12 months and 17 children over 24 months. Weight, height and BMI s.d. scores were calculated using 1990 UK Child Growth Foundation data. Vertebral BMAD and volumetric BMD (BMDvol) were calculated by Carter and Kröger algorithms respectively.
Results
Age of first treatment ranged from 0.57–5.6 years (mean $\pm$ s.d. $=3.45\pm1.50$). 81% (21/26) had type I OI; the remaining patients had type IV OI. There was no significant change in weight, height or BMI s.d. scores over 24 months. We observed an increase in age- and height-adjusted TBLH BMC (95%CI: 46.9, 232.5, $P=0.005$), LSBA (95%CI: 126.8, 359.1, $P<0.001$), LSaBMD (95%CI: 0.02, 0.216, $P=0.02$) and age corrected BMAD (95%CI: 0.0001, 0.013, $P=0.05$) over 12 months. From 12 to 24 months there was no change in height and age-adjusted bone measures. Total body fat mass (95%CI: 17.3, 657.5, $P=0.04$) and lean mass (95%CI: 446.5, 1490.8, $P=0.001$) significantly increased after 12 months of therapy but only lean mass continued to increase from 12 to 24 months (95%CI: 232.0, 1702.3, $P=0.01$). In the first 12 months, change in lean mass was associated with an increase in TBLH BA (95%CI: 0.04, 0.69, $P=0.03$) and TBLH BMC (95%CI: 0.22, 0.77, $P=0.004$).
Conclusions
Pamidronate had the greatest impact on size and age adjusted total body and lumbar bone mass in the first year of therapy. The increase in lean mass compared to fat mass was more significant in the first year of therapy and was associated with an increase in total body bone mass. Lean mass continued to increase in the second year. We speculate that improved mobility may underlie these findings.
Disclosure
The authors declared no competing interests.

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P119

Burden of disease in children with hypophosphatasia: results from patient-reported surveys

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Objectives
Hypophosphatasia (HPP) is a rare metabolic disease caused by loss-of-function mutation(s) in the tissue-nonspecific alkaline phosphatase (TNSALP) gene. Resultant low TNSALP leads to defective skeletal mineralization and diverse

complications that may include poor growth, proximal muscle weakness, pain, and compromised physical function in children. Here, we describe the burden of HPP in patients <18 years old as assessed by two surveys specific to HPP symptomology.
Methods
The Hypophosphatasia Impact Patient Survey (HIPS, internet-based) and the Hypophosphatasia Outcomes Study Telephone interview (HOST) were developed to characterize the burden of disease in patients with HPP. Answers consisted of yes/no, 'check all that apply,' and free text fields. Outreach from 2009–2011 by patient advocacy groups (HIPS, HOST) or physicians (HOST) provided awareness of the survey to patients or caregivers and invited participation. Data from questions common to both surveys were pooled for analysis. Results are expressed as percentage of patients who responded to each item.
Results
59 children (51% male; 75% caregiver responders) participated in the surveys (HIPS $n=44$; HOST $n=15$). Mean (standard deviation (S.D.)) age at survey was 7.6 (5.1) years; age at HPP onset was 0.8 (0.9) years. Skeletal abnormalities included abnormally shaped chest (54%, 32/59) and head (53%; 30/57), genu valgum (39%, 23/59) and genu varum (37%, 22/59). 42% (25/59) reported past fracture; 15% (9/59) reported >1 fracture. Muscle weakness (71%, 41/58), delayed walking (59%, 34/58), and unusual gait (57%, 25/44; HIPS only) were common. Pain (86%, 51/59) and recent pain (71%, 42/59) were prevalent. 51% (30/59) of children had required an assistive device at some point. At the time of survey, 38% (20/53) required a wheelchair, and 25% (13/53) required walking devices. In HOST, 73% (11/15) children reported difficulty climbing and descending stairs, and 12/12 children reported difficulty jumping. In HIPS, children reported using outpatient health services including physical (36%, 16/44) and occupational (23%, 10/44) therapy.
Conclusions
These patient/caregiver-reported data suggest children with HPP experience a high burden of disease and substantial morbidity that limits activities of daily living and quality of life. Additional studies are needed to fully elucidate the impact of HPP in children.
Disclosure
Scott Moseley, Eileen K Sawyer, and Tatjana Odrljin are employees of Alexion Pharmaceuticals, Inc., which funded and analyzed the HIPS and HOST studies. Thomas J Weber has received consulting fees from Alexion Pharmaceuticals, Inc. Priya S Kishnani has received honoraria from Alexion Pharmaceuticals, Inc and is chair of the HPP registry board.
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P120

Fracture incidence and bisphosphonate therapy in boys with Duchenne Muscular Dystrophy

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Background
DMD is a progressive neuromuscular disease often treated with oral glucocorticoids (GC) to prolong ambulation and maintain cardiovascular function. However, the osteotoxic GC effects often result in a skeleton prone to fractures. DMD boys presenting with fractures are treated with bisphosphonates (BP) but evidence of beneficial effects is limited. The aim of this work was to review the use of intravenous BPs in a group of severely affected boys with fractures.
Methods
Bone measurements by DXA, including size-adjusted lumbar spine BMD (LSBMAD), total body less head BMD (TBLHBMD) and vertebral fracture assessment were performed 12 months prior to, at start of BP therapy and 12 months later in 13, 18 and nine boys respectively.
Results
At the start of BP therapy, 12 boys were non-ambulant. 17 of the 18 boys were taking oral GC and vertebral fractures (VF) were identified in all. ten boys also suffered long bone fractures. In the group of 13 boys measured 12 months prior to BP treatment there were 35 VF (30 mild & five moderate) which increased to 59 (49 mild & 13 moderate) by the start of BP treatment. In the post treatment group of nine boys, there were 44 (34 mild & ten moderate) VF at start of BP therapy and the same number 12 months later. However, fracture severity had reduced to 39 mild & three moderate. Unfortunately, one of the moderate fractures identified before the start of therapy had deteriorated to a severe fracture during follow-up. Overall, after 12 months of BP therapy, remodelling was observed in 14 of the vertebrae and two incident fractures were identified. Although six boys were pre-treated with oral BPs, moderate VF were observed in all six at baseline. LSBMAD was within normal limits at baseline and did not change significantly at follow-up. In contrast TBLHBMD was reduced prior to treatment ($P<0.001$) but remained stable over the treatment period.
Conclusions
In this population, IV BPs appear to reduce fracture rate and severity. In contrast, oral BPs did not appear to protect against fracture. Importantly, for boys with DMD on long-term oral CS, LS BMAD was a poor marker of vertebral fragility.
Disclosure
The authors declared no competing interests.

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P121

A case of osteogenesis imperfecta mimicking the features of mucopolysaccharidosis IVA

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Background
Mucopolysaccharidosis IV is a rare, autosomal recessive disorder. Common presenting features include severe short stature, kyphoscoliosis, genu valgum, cloudy cornea, osteoporosis, mild coarsening of facial features, joint restriction in some large joints. Skeletal dysplasias should be considered in its differential diagnosis. Here we present a case whose initial diagnosis was Mucopolysaccharidosis IV and was diagnosed with osteogenesis imperfecta (OI) by COL1A2 mutation analysis.
Presenting problem
A 7-year and 9-month old girl was admitted for short stature.
Clinical management
Medical history revealed backpain and three fractures due to minor traumas. There was no parental consanguinity, no history of short stature and atraumatic fractures in the family. The height was 89.9 cm (−6.9 SDS), weight was 15 kg (−3.7 SDS). She had mildly coarse face, severe kyphoscoliosis and genu valgum. Teeth apperared translucent and sclerae were blue-grey. The hearing and intelligence were normal. She had slightly elevated ALP and mildly low 25OHD levels (298 IU/l, 16.4 ng/ml, respectively), laboratory tests were otherwise normal. X-rays revealed severe platyspondyly, bowing in the diaphysis of long bones and generalised hypomineralisation. She was diagnosed with MPS IVA in another center but in the follow-up period it was excluded with the normal enzymatic activity of N-acetylgalactosamine-6 sulfatase. In the light of her medical history and skeletal findings OI was considered. The mutation analysis revealed a heterozygous splice site mutation that substitution to A from G within intron 40 at c.2565+1 in the COL1A2 gene. Oral vitamin D3 and calcium was commenced prior to intravenous pamidronate treatment.
Discussion
The present mutation was reported to lead to OI. OI is a dominantly/recessively inherited disorder characterised with increased bone fragility due to low bone mass. The clinical features of disease is highly heterogenous. It is known that mutations in COL1A1 and COL1A2 have been identified in OI types I through IV. In a previous study the same mutation was showed in a patient with type IV OI. However the clinical findings of our case have confronted us in a quite different features. Therefore, we suggest that genotype- fenotype correlation is not clear in OI everytime.
Disclosure
The authors declared no competing interests.

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P122

Phalangeal microgeodic disease: A rare cause of painful swollen toes

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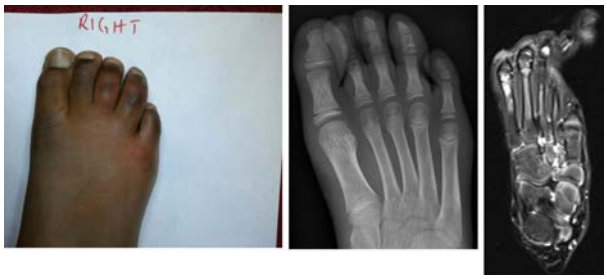
A healthy 8-year-old girl of Nigerian origin, presented in January 2014 with a 2 month history of progressive pain and swelling of the right 2nd, 3rd and 4th toe. There was no preceding trauma or illness. Those toes were swollen, tender and cold to touch, with bluish skin discoloration (Figure 1).
She had normal peripheral pulses. Her inflammatory markers were normal, as was haemoglobin electrophoresis. A Doppler ultrasound study ruled out vascular obstruction. X ray showed acro-osteolysis of the toes involved (Default 2). MRI revealed 'bone oedema' changes in the affected phalanges (MRI fat saturation image Figure 3).
She improved without any intervention in summer, which alongside the typical radiographic appearance, confirmed the diagnosis of Phalangeal Microgeodic Disease.



Figures 1-3

Repeat MRI in September showed almost complete resolution.
However the following November her toes became itchy, and by January 2015 they were swollen, painful and red again.
Phalangeal Microgeodic Disease is rare, with approximately 20 cases reported since the original description by Maroteaux in 1970. It usually affects the hands, whereas our case had foot involvement which is even rarer.
The aetiology is not clear, but cold exposure has been suggested as cases usually present in winter. Radiologic features typically show osteosclerosis with multiple small spots of osteolysis in the middle or proximal phalanx. MRI reveals evidence of bone marrow oedema.
Awareness of the diagnosis is important to prevent children being subjected to invasive investigations such as biopsy or inappropriate treatment such as antibiotics.
Disclosure
The authors declared no competing interests.

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P123

Does the introduction of vertebral fracture assessment change clinical practice?

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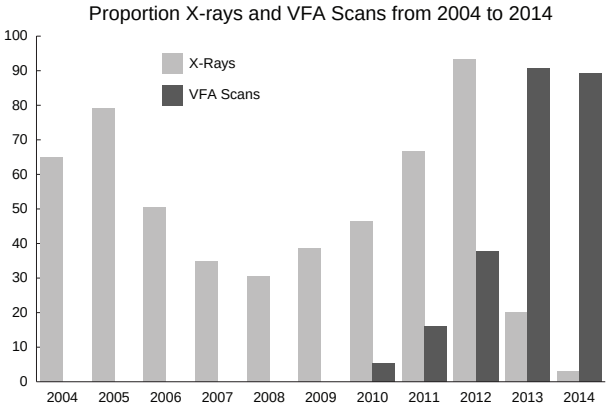
Introduction
Since the definition of osteoporosis in children changed following the revised ISCD guidelines of 2013, the presence of vertebral fractures has become more clinically important, in particular since vertebral fractures may occur despite apparently normal bone density (www.iscd.org). Although the detection of vertebral fractures in children is still largely dependent on lateral spine x-rays, the introduction of new higher resolution bone densitometry scanners has lead to the possibility of vertebral fracture assessment (VFA). We have reviewed our use of x-rays and VFA over the past 10 years to determine how VFA availability is leading to a change in clinical practice.
Methods
We reviewed x-rays and VFA scans in 163 children with osteogenesis imperfecta (OI) from 2004–2014 performed in a single centre. We calculated the proportion of children who had either a spine x-ray and/or VFA at the time of, or close to their annual DXA scan utilising either a GE Lunar Prodigy (2004–2010) or a GE Lunar iDXA (from 2010) bone densitometer.
Results
The attached figure shows a change in the proportion of spine x-rays (per DXA referral) of 65 to 93% from 2004 to 2010 and then a subsequent drop to 3% in 2014. The proportion of VFA scans increased from 5 to 89% between 2010 and 2014 with the most dramatic increase seen between 2012 and 2013.



Conclusion
The increase in proportion of spine x-rays from 2008 to 2010 reflects the increasing clinical importance of x-rays as a screening for asymptomatic vertebral fractures. However, the change in the proportion of VFA scans compared to x-rays in recent years reflects the availability and reliability of new generation DXA scanners. The added value of VFA scans is the significant reduction in radiation dose and increased convenience to the patients.
Disclosure
The authors declared no competing interests.

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P124

Bisphosphonate treatment and the characteristics of femoral fractures in children with osteogenesis imperfecta

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Objective
Bisphosphonates (BPs) are widely used in treatment of pediatric patients with osteogenesis imperfecta (OI) and their beneficial effect on bone density and fracture rates has been well reported. Atypical femoral fracture is a potential complication of bisphosphonates, usually occurring after several years of BP treatment in postmenopausal women. Some evidence suggests increased proportion of subtrochanteric femoral fractures in children with OI after prolonged use of bisphosphonates. The purpose of the present study was to assess whether BP treatment modifies the characteristics of femoral fractures in pediatric patients with OI.
Methods
This retrospective study included pediatric OI patients born between 1990 and 2012 and followed at Children's Hospital, Helsinki University Hospital, Finland. Altogether 93 patients were identified; all their femoral fractures that occurred before 31.12.2012 were analyzed using medical records. Radiographs were re-evaluated and the fractures were categorized by position and morphology and compared with the status of BP treatment.
Results
In total 168 femoral fractures had occurred in 32 patients (16 had OI type I, 8 type III, and 8 type IV); hospital records for 145 fractures were available. Of the fractures 46 had occurred during BP treatment, 20 during drug holiday and 79 in a patient naïve to BPs. At the time of fracture the mean age of patients was 6.7 years, range from week to 18.5 years and the mean duration of the BP treatment (if present) was 1.1 years, range from 1 day to 3.15 years. The level of fracture was proximal in 5.5%, subtrochanteric in 26.2%, mid or distal shaft in 49.7% and

distal in 18.6% of the cases. The morphology was transverse in 61.8%, oblique in 31.3%, and other (for example spiral or comminuted) in 6.9%. There were no correlation with former or present bisphosphonate treatment and fracture position or morphology.
Conclusion
Based on our findings BP treatment does not change the characteristics of femoral fractures in children with OI.
Disclosure
The authors declared no competing interests.
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P125

Vitamin D status of gastrostomy-fed children with special needs
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Background
Children with special needs may be greater risk of vitamin D deficiency due to decreased mobility and outdoor play, concomitant medications that increase catabolism of vitamin D, reduced nutritional intake and low body weight. Gastrostomy-fed children receiving a nutritionally complete formula may still be at risk of vitamin D deficiency due to the above factors.
Objective
The objective of this study is to assess the vitamin D status of special needs children receiving full or partial nutrition via gastrostomy.
Methods
Thirty-two children (24 males) aged 5–16 years, from seven special schools in Manchester receiving gastrostomy feeds took part in the study. Blood samples were obtained in March 2014 (end of winter) to evaluate serum levels of 25-hydroxyvitamin D (25OHD), calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), and parathyroid hormone (PTH). In addition, carers were interviewed to obtain a dietary history and assess the subjects' exposure to sunlight. Daily vitamin D intake was estimated from enteral feed nutritional data.
Results
All children had complex medical conditions. 26 were non-ambulatory and 18 were taking anti-epileptic drugs. Nineteen children (59%) had a Fitzpatrick skin type score of III or higher (South Asian or Black African ethnicity). The children had little or no sunshine exposure in the 3 months prior to data collection.
Data on serum 25OHD was available on 30 subjects and that on PTH in 25 subjects. The mean serum 25OHD concentration was 71.1 nmol/l ($\pm$21.4 nmol/l). One child was found to be vitamin D deficient (serum 25OHD 24.6 nmol/l) and four children were vitamin D insufficient (serum 25OHD range 29.9–47.9 nmol/l). Two out of 25 children (8%) had an elevated serum PTH above the upper end of the reference range. All children had normal serum concentrations of P, Ca, and ALP. Thirteen children received <10 μg of vitamin D/day from their feed (range 3.5–9.2 μg/day). None of the children were taking vitamin supplements. Dietary calcium intake met the recommended intake for age and gender in all but one subject.
Conclusion
From our results we conclude that nutritionally complete gastrostomy feeds may be protective against vitamin D deficiency in gastrostomy-fed children with special needs.
Disclosure
The authors declared no competing interests.
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P126

Low bone mass in children with epidermolysis bullosa
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Background
Epidermolysis bullosa (EB) is a rare, genetic skin disorder characterized by increased skin fragility after relatively minor trauma. It varies in severity even within the same subtype, ranging from a minor inconvenience to a severely disabling or life threatening disorder. In generalized forms, EB is a systemic disorder in which osteoporosis is a frequent manifestation.
Presenting problem
While the mutations that cause EB do not have a direct effect on the bone, various risk factors contribute to low bone mass in children with generalized EB. These include i) reduced mobility mainly due to wound pain and contractures, ii) malnutrition caused by eating problems on the one hand, and elevated needs of calories, minerals and proteins on the other hand, iii) chronic inflammation due to persisting wounds leading to the production of cytokines which influence bone health, iv) delayed puberty and growth, and v) insufficient sun exposure due to bandages and wound dressings and because of the delicate nature of the skin.
Clinical management
Diagnosis of osteoporotic fractures tends to be late, as patients with generalized types of EB frequently suffer from chronic pain. DXA scans seem to be useful only when symptoms exist. X-ray images and laboratory values are also important for diagnosis.
Multifactorial prevention is essential to at least reduce bone involvement. Weight bearing activities, adequate nutrition, treatment of inflammation, and vitamin D supplementation are major aims in prevention.
Therapy of fractures is multidisciplinary as well, consisting mainly of the improvement of the management of risk factors and administration of bisphosphonates.
Discussion
Low bone mass in generalized forms of EB is frequent. Reduced mobility seems to be the main risk factor. In addition to promoting weight-bearing activities and adequate nutrition, prevention strategies such as hormone therapy to promote growth and puberty are discussed.
Disclosure
The authors declared no competing interests.
DOI: 10.1530/boneabs.4.P126

P127

The outcomes of a standardized approach to managing metabolic bone disease of prematurity
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Metabolic bone disease (MBD) of prematurity is a well-recognized complication of preterm birth. Yet there is limited evidence for the optimal assessment, monitoring, and subsequent bone health management.
Retrospective audit of 171 infants born <32 weeks' gestation between November 2012 and January 2014 at three Monash Health neonatal units (Melbourne, Australia) was undertaken. Infants had mean gestational age (GA) 28.6$\pm$2.1 weeks and birth weight (BW) 1190$\pm$374 g. Identified MBD risk factors include intrauterine growth retardation (IUGR; $n=33$, 19.3%), maternal pre-eclampsia ($n=17$, 9.9%), necrotising enterocolitis (NEC; $n=9$, 5.4%), and medication exposure: methylxanthines (94.2%; mean 54.8days), diuretics (38.6%; mean 49.2days) and glucocorticoids (5.3%; mean 35days). Infants received an average 19.8 days of total parenteral nutrition (TPN), with majority on fortified expressed breastmilk once enteral feeding established.
84.8% infants had initial MBD screen (mean age 36.3 days) with only 45% of the total cohort having repeated monitoring (mean age 71.9 days). 14.2% had alkaline phosphatase (ALP) levels >500 U/l initially, reducing to 10.1% on follow-up. All infants received at least vitamin D 400 units/day. 25.1% ($n=43$) commenced phosphate supplements (mean 46.3 days) and 19.9% ($n=34$) commenced calcium supplements (mean 31 days).
Average birth length was 37.7$\pm$5 cm with evidence of slowing growth velocity compared to reference charts (mean follow-up length 51.8$\pm$9.5 cm at mean age 118.6 days). Fractures identified from clinical documentation include birth trauma related fractures ($n=2$), suspected non-accidental injury diagnosed post-discharge ($n=2$), and one infant with multiple MBD risk factors. Rate of fractures may be underestimated given that radiological evidence was not included in this audit.
Comparing phosphate-treated and untreated groups revealed significant difference ($P<0.001$) for GA and BW: 26.7$\pm$1.7 weeks, 918$\pm$272 g for treated vs 29.2$\pm$1.9 weeks, 1283$\pm$359 g for untreated. In the phosphate-treated group, both mean ALP (pre-treatment 467$\pm$204 U/l and post-treatment 342$\pm$221 U/l, $P\leq0.01$) and mean phosphate levels improved (1.8$\pm$0.4 mmol/l vs 2.2$\pm$1.0 mmol/l, $P<0.01$). Linear growth difference between phosphate-treated ($n=10$) and untreated ($n=24$) was insignificant at >6 months age ($P=0.13$), although this may reflect limited data.
Further evaluation is anticipated to improve MBD understanding in this high-risk cohort particularly given morbidity associated with occult fractures. Simplifying the MBD protocol to key components (ALP and phosphate) would allow for more cost-effective surveillance.
Disclosure
The authors declared no competing interests.
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P128

Patients treated with anti-epileptic drugs have a higher rate of fracture and impaired bone and muscle development compared with controls: results from a pilot study

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Epilepsy is a relatively common condition of childhood, with anti-epileptic drugs (AEDs) the mainstay of medical therapy. AED use in adults has been shown to be associated with impaired bone density and increased risk of bone fracture. Paediatric data are more limited particularly in relation to fracture risk and skeletal geometry.

This study aimed to examine the within-pair differences in fracture prevalence and bone, muscle and balance parameters in sex-matched twin, sibling or first cousin pairs who were discordant for exposure to AED therapy, as a case-control, cross sectional study. Subjects were aged 5–18 years and had taken AEDs for at least 12 months. Members of each pair were aged-matched to within 2 years of each other. Questionnaires were used to obtain information about medical history, epilepsy history, bone health, and activity levels. Bone health was assessed using dual energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT). For muscle force and balance parameters, the Leonardo ground force reaction platform (GFRP) was utilised. Serum 25-hydroxyvitamin D levels (25OHD) levels and bone age were also assessed.

A total of 23 matched pairs were recruited (seven twin, 14 sibling, and two cousin pairs). AED users showed an increased prevalence of fractures ($n=15$ vs 4 in control subjects), particularly at the distal radius. Concordantly, trabecular volumetric bone mineral density (vBMD) measured by pQCT at the 4% site of the tibia was reduced by 14% ($P=0.02$) in AED users. This was coupled with the finding that AED users exert a decreased maximum force (Fmax) on the tibia as measured by Leonardo GFRP. There were no within-pair differences in bone mineral parameters measured by DXA; however, AED users showed a tendency towards decreased total and trabecular area at the 4% tibia and polar strength-strain index as revealed by pQCT. There was no balance impairment evident in the AED users in comparison to controls.

AED users therefore experienced more fractures and were found to have reductions in volumetric bone density and muscle force compared to their matched controls. These results suggest that those on AEDs have impairment in the muscle–bone unit and therefore have relative skeletal fragility. Future studies designed with a longitudinal approach are required to confirm these findings.

Disclosure

The authors declared no competing interests.

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P129

Cortical area and volumetric density during pubertal growth: longitudinal analysis in black and white South African adolescent males

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Skeletal development during childhood and adolescence is an important determinant of adult bone health. Patterns of growth differ between populations, but it is unclear how these differences relate to changes in bone size and volumetric density. We aimed to examine ethnic differences in skeletal phenotype in the context of pubertal growth and development in 279 adolescent males from Johannesburg, South Africa.

We performed annual peripheral quantitative computed tomography (pQCT) at the 38% tibial site between the ages of 12.3 and 22.2 years. Outcome measures were volumetric bone mineral density (vBMD) and cortical cross-sectional area (CSA). Changes in each bone parameter and height were modelled longitudinally using superimposition by translation and rotation (SITAR),[1] stratified by ethnicity. The age at peak velocity (APV) was estimated from the individual growth curves, and these ages were compared within and between groups using two-sample t-tests.

Mean height APV was 13.7 (s.d. 1.0) years in black males and 12.7 (0.8) years in white males (difference $P<0.01$). Mean APV for cortical CSA was 13.2 (1.1) and 12.9 (0.8) years respectively ($P=0.06$). Peak changes in cortical CSA preceded the pubertal growth spurt by an average of 6 months in black males, but occurred 3 months after peak height growth in white males. Mean APV for vBMD was 14.8 (1.2) years in black males and 14.0 (1.0) years in white males ($P<0.01$), an average of 13 and 16 months after peak height velocity respectively. Changes in vBMD during growth could represent reduced bone turnover or infilling of the Haversian systems.

The delay between peak changes in cortical CSA and vBMD suggests a period of consolidation during which mineral is deposited primarily within the existing cortical envelope rather than only on the bone surfaces. The mean delay was significantly longer among black males (19 months) than among white males (13 months) ($P<0.01$). This may reflect ethnic differences in mineral metabolism, or may be related to differing environmental influences such as nutrition and physical activity. These possible determinants of timing in skeletal growth will require further investigation, as will the implications for adult bone health.

Disclosure

The authors declared no competing interests.

Funding

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Reference

1. Cole T *et al*. *Int J Epidemiol* 2010 **39** 1558–1566.

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P130

Chronic recurrent multifocal osteomyelitis: the value of whole-body MRI in a series of 34 children

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Objectives

To assess the role of whole-body MRI in the diagnosis and management of chronic recurrent multifocal osteomyelitis (CRMO) is a benign and non-infective auto-inflammatory bone disorder characterised by multiple and recurrent inflammatory bone lesions. No universal diagnostic criteria exist.

Methods

Retrospective review of CRMO cases diagnosed at this hospital between 2008 and 2014. Cases were identified from patient records and clinical information was collated from radiology and histopathology records and individual case notes.

Results

Forty-seven CRMO cases were identified who had had whole-body MRI, of these 34 cases were children. The number of whole-body MRI scans per case ranged from 1 to 5. Whole-body MRI identified multifocal lesions were found most frequently in the clavicle, tibia and femur. All cases were managed with non-steroidal anti-inflammatory and/or bisphosphonate medication. No cases received steroid or anti-TNF treatment.

Conclusion

In the absence of specific diagnostic criteria, whole-body MRI in combination with clinical assessment can make the diagnosis of CRMO. Whole-body MRI has almost entirely replaced biopsy in the diagnosis of CRMO at our institution.

Disclosure

The authors declared no competing interests.

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P131

Association between serum 25-hydroxyvitamin D and incidence of infections in 6–12 years old children in a semi-rural setting in Western Maharashtra, India

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Objectives
Previous studies have shown that burden of infections is greater in those with low body stores of vitamin D. Vitamin D is a key mediator of innate immunity and is crucial in production of cathelicidin, a potent antimicrobial agent. Vitamin D deficiency is common among Indian children; the prevalence of infections is high. Thus, aims of our study were to examine the association between: i) serum 25-hydroxyvitamin D (25OHD) concentrations and symptoms of infections and ii) 25OHD and cathelicidin concentrations in 6–12 years old in a semi-rural setting.
Methods
Cross-sectional study carried out in 432 children (6–12 years) in a primary school in a semi-rural area near Pune, India (18°N). Information on infection-related symptoms during the preceding fortnight was collected using a validated questionnaire administered to parents and children. Biochemical assessments included serum 25OHD (EIA Kit, DLD Germany) and cathelicidin (on a sub-sample of 160; EIA Kit, Cusabio).
Results
Mean 25OHD concentrations were 23.4 ± 4.2 ng/ml; 32% children had vitamin D deficiency with 25OHD $\leq$20 ng/ml (IOM 2011). 25OHD concentrations were positively correlated with cathelicidin levels ($r=0.3$; $P<0.01$). Respiratory symptoms were reported by 49%, fever by 35%, gastrointestinal infections by 21%, skin infections by 15%, and other infections (ocular, urinary) by 17% (Fig. 1). No correlation was found either between serum 25OHD or cathelicidin and the infection-related symptoms reported by subjects.

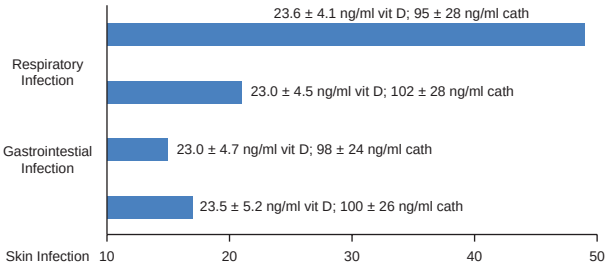

Figure 1 Percentage of infection-related symptoms with mean ± s.d. of 25OHD and cathelicidin concentrations.

Discussion
We found that vitamin D status of children was not associated with their infection related symptoms, possibly as over two-thirds of children were vitamin D replete, with 25OHD concentrations $\geq$20 ng/ml.
Disclosure
The authors declared no competing interests.
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P132

Bone structural characteristics and response to bisphosphonate treatment in children with Hajdu–Cheney syndrome

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Objectives
Hajdu–Cheney syndrome (HCS) is an ultra-rare, genetic bone disease caused by mutations in the *NOTCH2* gene. HCS is characterised by dysmorphic features, acroosteolysis, and high turnover osteoporosis. Sparse evidence in adult HCS suggests increased BMD and reduced bone turnover during bisphosphonate (BP) therapy. A single paediatric case report indicated beneficial effects of i.v. pamidronate therapy. We present four paediatric patients with HCS, their bone histomorphometric and bone geometric characteristics, and their response to BP therapy.
Methods
Four children with HCS (one female and three males), presented to endocrinologists with severe osteoporosis at the ages of 6.5, 10, 14.5, and 15.5 years. Iliac crest bone biopsies and peripheral quantitative computed tomography (pQCT) were available in two subjects. Their response to various BP therapy regimens (pamidronate, zoledronic acid, and alendronate) was monitored using DXA ($n=4$) and forearm pQCT ($n=2$), over 2–3.5 years of continuous treatment.
Results
All children had sporadic mutations and demonstrated typical phenotypic characteristics of HCS but also features not previously described such as delayed puberty, intestinal malrotation, and hip acetabular dysplasia. Histomorphometric results demonstrated increased amount of trabecular bone and increased bone turnover, with normal bone formation indices. pQCT revealed normal trabecular density but very low cortical density *Z*-scores (−4.3; −4.9), which increased during i.v. BP therapy. In addition, after 1 year of therapy, median size-corrected lumbar spine BMD *Z*-scores increased from −1.328 to −1.013.
Conclusion
Increased trabecular bone volume and bone turnover, normal bone formation, and low cortical density were characteristic features in our HCS cohort. These features are consistent with the effect of activating *NOTCH2* mutations which cause osteoblast proliferation, as well as increased osteoclastogenesis. I.v. BP therapy increased size-corrected lumbar spine BMD and radial cortical density, which provides evidence of beneficial effects in children with HCS. Whether acroosteolysis can be improved with BP therapy remains to be elucidated.
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Disclosure
The authors declared no competing interests.
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P133

Fibrodysplasia ossificans progressiva: disabling but now treatable

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Background
Fibrodysplasia ossificans progressiva (FOP) is a rare condition characterised by congenital malformation of the great toes and progressive heterotopic endochondral ossification. The disease progresses with episodic flare-ups, resulting in disabling cumulative immobility. The discovery of the *ACVR1* gene as the cause of FOP has allowed identification of therapeutic targets.

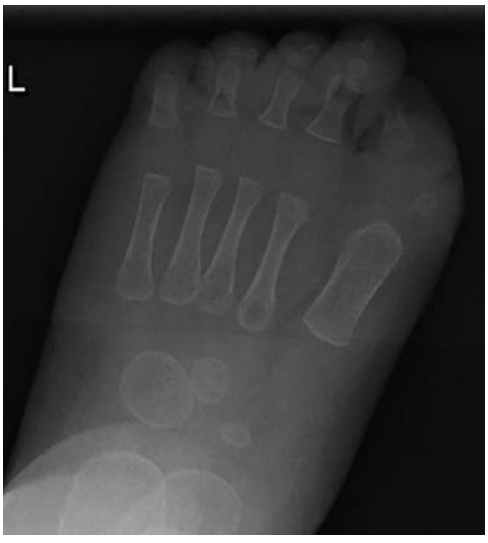

Figure 1 Radiograph of Hallux valgus at 6 months of age.

Palovarotene, a retinoic acid receptor gamma agonist, is in phase 2 clinical trials.
Presenting problem
A 7-year-old boy with Hallux valgus, recurrent painful episodes of soft tissue swelling and new abnormal bone formation.
Clinical management
Review of radiographs taken in infancy (Fig. 1) revealed the diagnosis of FOP. This had not been previously recognised, although he had been seen in a Hallux Valgus Clinic. CT of his neck showed subcutaneous ossification in the superficial cervical soft tissues posterior to the C4 – T1 spinous processes measuring 2.3×1.3×5.3 cm (arrow in Fig. 2).

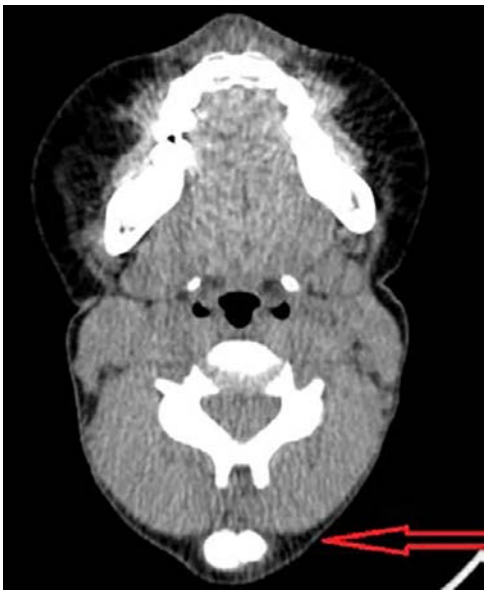

Figure 2 CT scan of neck, arrow points to ossification posterior to cervical spine.

Discussion
As specific treatments are becoming available for FOP, neonatologists, paediatricians, and orthopaedic surgeons should consider the diagnosis if a baby or child presents with bilateral Hallux valgus or episodes of swelling with evidence of ossification. These children should now be referred to a paediatric metabolic bone clinic to consider genetic testing and for further specialist management.
Disclosure
The authors declared no competing interests.
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P134

Associations of 25-hydroxyvitamin D with major components of metabolic syndrome in children
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Objective
To study any possible relations of vitamin D status and metabolic syndrome (MetS) components in children, since there is evidence for extraskeletal functions of vitamin D, and its deficiency may contribute to the pathogenesis of several major diseases. In addition to explore any possible role of birth weight (BW).
Methods
Clinically healthy children aged 3–9 years ($n=152$) were included in the study. Forty-six were born large for gestation age (LGA), 71 appropriate (AGA), and 35 small for gestational age (SGA). The parameters determined in serum were 25OHD and the components of MetS in children of fasting insulin (I_F) and glucose (G_F), HDL cholesterol (HDL-C), and triglycerides (TGs). All blood samples were taken during winter months (December–April). Waist circumference (WC) and systolic and diastolic blood pressure (SBP/DBP) were measured. The homeostatic model assessment for insulin resistance (HOMA-IR) and BMI Z-score were calculated. Birth weights were also recorded.
Results
Multivariate regression analysis of 25OHD and the variables determined after adjustment for gestational age (GA), birth weight, age, sex, and BMI Z-score revealed that 25OHD circulating levels were inversely associated with WC Z-score ($R=-0.22$, $P=0.03$, 95% CI -10.4, -0.4) and SBP ($R=-0.22$, $P=0.03$, 95% CI -0.6, -0.02). Their association with HOMA-IR was approaching significance ($R=-0.18$, $P=0.08$, 95% CI -22.52, 1.26), but none was found with TGs or I_F. Positive associations were found with HDL-C ($R=0.22$, $P=0.02$, 95% CI 0.04, 0.4), and unexpectedly with DBP ($R=0.29$, $P=0.006$, 95% CI 0.16, 0.8), and G_F ($R=0.22$, $P=0.03$, 95% CI 0.03, 0.56). All these associations were independent of GA, age, and BMI Z-score but were dependent on birth weight. An inverse relationship was also observed between 25OHD levels and birth weight ($R=-0.2$, $P<0.05$).
Conclusion
It seems that in prepubertal children birth weight may affect associations of vitamin D status with some major known components of MetS.
Disclosure
The authors declared no competing interests.
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P135

Chronic recurrent multifocal osteomyelitis in children: a new, MRI-based method of quantifying inflammation in the bone
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Objectives
The main aim of the study is to describe a new method of quantitative, MRI-based assessment of inflammation in children with chronic recurrent multifocal osteomyelitis (CRMO).
General hypothesis
The main hypothesis is that the bone marrow edema, as detected in CRMO with MRI, can be quantified to aid early diagnosis and help identify clinically silent lesions.
Methods
We performed a retrospective analysis of static MRI scans from six children with CRMO at the Royal National Orthopaedic Hospital. Five of the patients were female and one male. They were 4–14 years of age and they all had multiple lesions on whole-body MRI. The MRIs were further analysed with a specialized computer software. Analysis of static MRI (STIR) was based on a computer-guided, manually selected, region-of-interest (ROI) method, and quantitative, pixel-by-pixel processing was performed. We looked at the bone marrow signal intensity (SI), described as bone marrow edema (BME) in conventional fat suppression STIR sequences. We calculated the changes in intensity from BME lesions (lesion MI–mean intensity), to areas of healthy bone marrow from the same patient as internal control (internal control MI–mean intensity). This calculation is presented as ratio (lesion MI by internal control MI) and also as percentage changes.
Results
There is a persistent increase in signal intensity in the areas of bone marrow edema, compared to control, ranging from 1.26 to 3.35 ratio (mean 2.25), corresponding to percentage changes from 25.67 to 235.06% (mean change 125.41%). Our results show that this method can detect bone inflammation with at least the same sensitivity as STIR MRI. They also show that it is possible to capture inflammatory bone lesions that have gone undetected in conventional MRI, which are depicted as 'hot spots'. Finally, they show various degrees of intensity of the inflammatory process, which can be used to 'titrate' inflammation in the bone.
Conclusions
This method can detect and titrate inflammation from bone marrow edema lesions. Further research is needed to formally evaluate the sensitivity and specificity of the method.
Disclosure
The authors declared no competing interests.
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P136

A modified performance-oriented mobility assessment tool for assessing clinically relevant gait impairments and change in children with hypophosphatasia: development and validation

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Objective
Mobility is an important endpoint in patient care with implications for activities of daily living, community participation, and quality of life. We adapted the performance-oriented mobility assessment (POMA-G),[1] a widely used and validated clinical gait assessment tool for adults, to use in children with hypophosphatasia (HPP). HPP is the rare metabolic disease caused by loss-of-function mutation(s) in the gene encoding tissue non-specific alkaline phosphatase. HPP manifests a broad spectrum of complications in children, which may include rickets and proximal muscle weakness.
Methods
The 12-point POMA-G (12, no impairment and 0, greatest impairment) was chosen as a potential measure of clinically meaningful musculoskeletal impairments in children with HPP because the majority of components (including trunk sway, walking stance, and step and gait assessments) directly or indirectly measure defects seen in HPP. The POMA-G was modified (modified performance-oriented mobility assessment (MPOMA-G)) to focus on its components most relevant to HPP while increasing utility in video analysis. Three trained physical therapists scored archival videos of walking from an HPP natural history database[2] using MPOMA-G. Intraclass correlation coefficients (ICCs) were calculated to assess inter-rater agreement. The relationship between MPOMA-G scores and other clinical outcome measures available in these patients (Childhood Health Assessment Questionnaire (CHAQ) Disability Index, Pediatric Outcomes Data Collection Instrument (PODCI) Transfer and Mobility Scale, 6-Minute Walk Test (6MWT)) was determined through linear regression.
Results
Modifications to the POMA-G included: removal of gait initiation (less sensitive for children with musculoskeletal disorders) and path assessment (limited utility in single point-of-view video); increasing step length and step continuity from two- to three-point scales to improve sensitivity to detect change; and, clarifying descriptions of components such as Trunk sway to increase sensitivity and consistency amongst raters. Inter-rater agreement across all patient-visits was strong (ICC = 0.76, $P < 0.0001$). Linear regressions between MPOMA-G and other clinical endpoints resulted in r^2 values of 0.73 (CHAQ; 21 datapoints), 0.53 (PODCI; 21 datapoints), and 0.70 (6MWT; 28 datapoints).
Conclusions
The MPOMA-G is a reliable and valid measure for detecting clinically significant impairments in gait in videos of children with hypophosphatasia. This tool should be evaluated further for direct implementation in the clinical setting.
Disclosure
D Phillips received consulting fees from Alexion Pharmaceuticals, Inc. M Vallée and K P Fujita are the employees of Alexion Pharmaceuticals, Inc. K L Madson has received honoraria from Alexion Pharmaceuticals, Inc. M P Whyte has received honoraria, research grants, and travel support from Alexion Pharmaceuticals, Inc.
References
1. Tinetti *Am J Med* 1986.
2. Whyte *JMBR* 2014 **29** (Suppl 1).
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P137

A slow and difficult diagnosis of a child with chronic recurrent multifocal osteomyelitis

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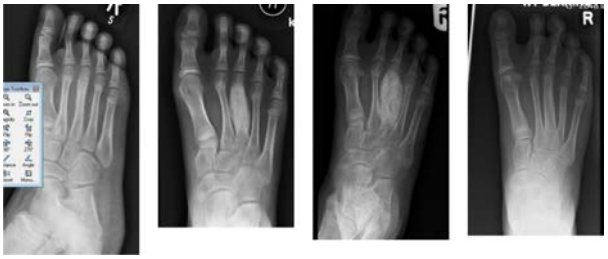
Background
Chronic recurrent multifocal osteomyelitis (CRMO) is an auto-inflammatory bone disorder that has been difficult to diagnose in the past. Diagnosis used to depend on bone biopsy but can now be made with whole-body MRI scan.
Presenting problem
A 9-year-old healthy girl had a 2-year history of pain, swelling, redness and heat in her right foot following a fall from bars in the park. She had an X-ray of her foot on the day of injury which was reported to be normal (Fig. 1).
The pain and swelling persisted and she had a repeat X-ray (Fig. 2), MRI scan, blood tests and a bone biopsy at her local hospital, which ruled out malignancy. After a year her foot was still swollen and painful and she was unable to walk far. Her right middle metatarsal was inflamed and tender on palpation, and she walked with a limp. Blood tests showed raised ESR and X-ray of right foot showed periosteal reaction (Fig. 3). A month later X-ray showed more expansion of the lesion encompassing the whole of the diaphysis. She had a CT scan, a second biopsy, chest X-ray, and skin tests to rule out tuberculosis.
Clinical management
She was referred to the paediatric metabolic bone clinic where a whole-body MRI scan was requested and showed signs of CRMO.
She was treated with i.v. pamidronate 3 monthly for three cycles, which led to a dramatic improvement in symptoms, clinical signs and radiological appearance (Fig. 4).



Figures 1–4

Discussion
This case shows that whole-body MRI scan can make the diagnosis of CRMO and that pamidronate treatment can be dramatically effective.
Disclosure
The authors declared no competing interests.
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P138

In-depth phenotyping including analyses of skin connective tissue in osteogenesis imperfecta

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Osteogenesis imperfecta (OI) is a heterogeneous group of inherited disorders of bone formation, resulting in low bone mass and an increased propensity to fracture. Over 90% of patients with OI have a mutation in *COL1A1*/*COL1A2*, which shows an autosomal dominant pattern of inheritance. Several other genes are associated with the autosomal recessive forms of OI. In-depth phenotyping and in particular, studies involving manifestations in the skin connective tissue have not previously been undertaken in OI. With increasing use of genomics in clinical practice, it becomes even more important to have extensive phenotyping data in order to make meaningful interpretation of variants identified through these studies.
As part of the rare diseases in bone, joints and/or blood vessels (RUDY) study, in collaboration with the NIHR Rare Diseases Translational Research Collaboration, we undertook a national study of skin biopsies in patients with OI. The plan was to perform ultrastructural examination and phenotype-based assays of the skin connective tissue in patients with OI; to enable use of results in the diagnostic work-up of OI.
From a previous pilot study done in Sheffield, we know that there are important indicators on electron microscopy of identifying a pathogenic mutation in *COL1A1/A2* (Balasubramanian *et al*. *Clin Dysmorphol* 2014). As part of this larger study, we studied the manifestations in the skin connective tissue and undertook in-depth clinical and molecular phenotyping of patients with OI. This in combination with phenotype-based assays on cultured fibroblasts have provided more insight into the pathways to direct gene testing and reinforced the need for accurate phenotyping in conjunction with genomic analyses.
Disclosure
The authors declared no competing interests.
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P139

Abstract withdrawn.

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P140

Rickets in two patients pediatrics

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The Rickets is a disease which disturbs normal bone formation through different methods, like vitamin D deficiency, malabsorption, chronic renal disease, metaphisary dysplasia, low phosphorus and resistant rickets.
The peak age at which rickets is most prevalent is usually 3–18 months, and the characteristic clinical features of this metabolic bone disease include enlargement of the epiphyses of the long bones and rib cage, bowing of the legs, bending of the spine, and weak and toneless muscles. In the past, severe rickets entailed severe deforming and debilitating bone disease.
To describe two patients pediatrics with rickets entailed severe deforming and debilitating bone disease, and the biochemical characteristics are table 1.

Table 1

Age	Sex	Calcio (mg/dl)	fosforo	PTH (pg/ml)	Alkalin fosfatasa (UL)	25OHVI-TAMINA D (ng/ml)	1.25OH-VITA D	Densitometry L4	Type
6	Boys	5.37	5.4	212	2049	12.8	15	−4.2 DE	Carencial
9	Girls	7.3	5	163	1311	20.2	295	−6 DE	type II rickets

Exogenous vitamin D deficiency is the most frequent cause of rickets. It is linked to two fundamental facts that can act independently or simultaneously: limited sun exposure and vitamin D deficiency in the nutrition. Besides the vitamin D deficiency, calcium deficiency and acquired and inherited disorders in vitamin D, calcium and phosphorus metabolism are also causes of rickets.
Disclosure
The authors declared no competing interests.

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P141

Persistence of musculoskeletal abnormalities in children and adolescents with inflammatory bowel disease: a prospective longitudinal study

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Objectives
To evaluate musculoskeletal development using pQCT and DXA in childhood onset inflammatory bowel disease (IBD).
Methods
Prospective longitudinal study with 12 months follow-up in 43 children (23 males) with IBD: 30 crohn's disease(CD), 13 ulcerative colitis (UC) and inflammatory bowel disease unclassified (IBDU). pQCT at 4% and 66% radius, DXA for total body (TB), lumbar spine (LS) bone mineral content were assessed at baseline and 12 months. pQCT parameters for area and circumference were adjusted for height. DXA BMC was adjusted for bone area. Results reported as median (range).
Results
In CD, 3/30 (10%) and 4/30 (13.3%) were on oral Prednisolone at baseline and 12 months. In CD, 2/30 (6.7%) and 8/30 (26.7%) were on anti-TNF therapy at baseline and 12 months. In UC/IBDU, 2/13 (15.4%) and 3/13 (23.1%) were on oral Prednisolone at baseline and 12 months. In UC/IBDU, 0/13 and 1/13 (7.7%) were on anti-TNF therapy at baseline and 12 months. No child had surgical resection during follow-up.

Table 1

	CD baseline (*n*, 30)	CD 12 months (*n*, 30)	*P* value	UC/IBDU baseline (*n*, 13)	UC/IBDU 12 months (*n*, 13)	*P* value
Age (years)	13.8 (10.4, 16.5)	14.8 (11.5, 17.6)	–	13.2 (9.8, 15.8)	14.2 (10.8, 16.7)	–
Ht for bone age *Z* score	−0.1 (−2.1, 2.7)	−0.1 (−2.4, 2.2)	0.51	0.0 (−1.7, 2.6)	−0.2 (−2.2, 1.1)	0.65
Pre-pubertal	6/30 (20%)	1/30 (3%)	–	3/13 (23%)	2/13 (15%)	–
Early/mid puberty	11/30 (37%)	14/30 (47%)	–	8/13 (62%)	7/13 (54%)	–
Late puberty	13/30 (44%)	15/30 (50%)	–	2/13 (15%)	4/13 (31%)	–
ESR (mm/h)	13 (1, 102)	12 (1, 70)	0.80	17 (7, 42)	14 (6, 47)	0.87
Remission/mild disease	30/30 (100%)	28/30 (93%)	–	12/13 (92%)	12/13 (92%)	–
DXA						
TB BMC (bone area) *Z* score	−0.3 (−0.7, 0.8)	−0.3 (−0.7, 0.6)	0.21	−0.1 (−0.7, 0.8)	−0.2 (−1.0, 0.9)	0.45
LS BMC (bone area) *Z* score	0.3 (−1.3, 1.4)	−0.5 (−1.6, 1.2)	0.10	0.5 (−1.3, 1.2)	−0.2 (−1.0, 0.9)	0.91
PQCT						
Volumetric BMD *Z* score	−1.0 (−2.8, 1.2)	−1.3 (−2.9, 2.8)	0.19	−1.0 (−2.6, 2.0)	−1.0 (−2.7, 1.3)	0.20
Trabecular BMD *Z* score	−0.9 (−3.9, 1.4)	−0.8 (−3.5, 2.7)	0.60	−0.7 (−2.9, 2.5)	0.3 (−2.5, 2.7)	0.20
Cortical BMD *Z* score	−1.2 (−5.2, 2.0)	−0.2 (−3.6, 2.0)	0.05*	−0.9 (−3.7, 1.7)	−0.7 (−3.9, 1.9)	0.35
Periosteal circumference *Z* score	−1.1 (−2.8, 1.9)	−0.6 (−5.2, 2.1)	0.72	−0.4 (−2.6, 1.6)	−0.7 (−2.4, 0.5)	0.01*
Endosteal circumference *Z* score	2.8 (0.9, 5.0)	2.6 (−1.2, 5.1)	0.72	3.5 (−0.7, 0.8)	3.4 (1.5, 6.2)	0.17
Muscle area *Z* score	−1.7 (−4.3, 0.1)	−2.3 (−7.9, −0.1)	0.40	−2.0 (−3.2,1.5)	−2.4 (−3.0, 0.8)	0.19

There were no gender differences in changes in DXA, pQCT parameters in both IBD sub-groups. Baseline IGF1:IGFBP3 *z*-score was associated with change in volumetric BMD ($r=0.42$, $P=0.02$).
Conclusion
Despite relatively mild disease and pubertal progression, children with IBD have persistent abnormal bone geometry suggestive of reduction in cortical thickness. With follow-up, trabecular BMD appears to be more affected in those with CD, whereas cortical BMD was more affected in UC/IBDU. Long term follow-up studies of bone development in childhood onset IBD and the relationship with the GH-IGF axis are needed.
Disclosure
The authors declared no competing interests.

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P142

The mechanical multi-stimulation for musculoskeletal disease

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Osteoporosis takes the form of porous bone loss which is due to aging, insufficient exercise and unbalanced nutrition and so on. A number of treatments were developed to treat the osteoporosis, which were categorized by pharmacological and non-pharmacological methods. However, it is generally accepted that taking too much pharmacological medication may be harmful to the health. Thus, non-pharmacological treatments are considered as the alternative ways to overcome the side effects of pharmacological medication. Moreover, non-pharmacological treatments, such as vibration, laser, and ultrasound therapy, would be more easily applied to old people, disabled person, patients. The principle of physical stimuli effect could explain by mechanostat and daily stress. Therefore, the aim of this study is to evaluate the effects of mechanical multi-stimulation applied on the mice tibia with morphological characteristics. Twenty five female C57BL/6 mice (12-weeks-old) were used for the experiment. The study was carried out on five groups (control; Con, Laser, Vibration; Vib, Ultrasound; Ultra, and Multi Stimulation; MS) of animals each consisting of five mice. Five groups of mice were ovariectomized to induce osteoporosis. Animals were scanned at 0 and 6 weeks after ovariectomy by using micro computed tomography to estimate morphological characteristics of tibial trabecular bone. Morphological analysis showed that structural parameters of multi-stimulation group appear better phase in BV/TV, Tb.Th, Tb.N, Tb.Sp, SMI, and Conn.Dn than sham even single stimulation groups. We evaluated the effects of multi-stimuli for treatment or prevention of osteoporosis. Taken together, the results showed that multi-stimuli

could suppress the continuous progress of bone deterioration, thinning and disconnectivity than single stimulus and sham group. This study suggests that multi-stimulation may restrain the change as the degenerate phase on osteoporosis in the mice tibia.

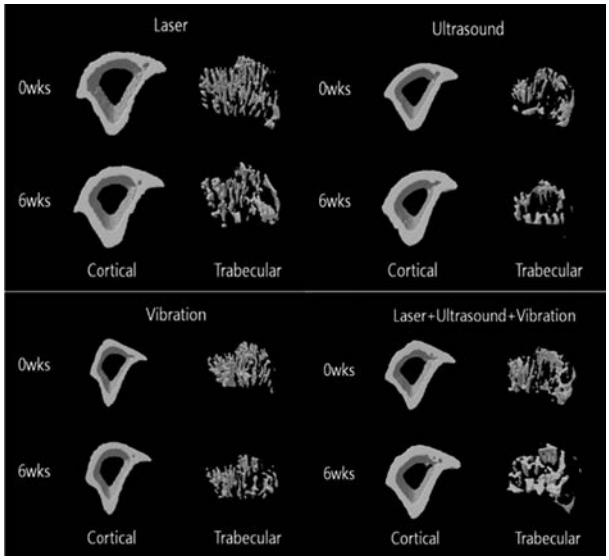

Figure 1 The changes of cortical and trabecular bone of tibia.

Disclosure
The authors declared no competing interests.
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P143

Low serum vitamin D levels in children treated for hematologic oncologic diseases

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Objectives
Vitamin D deficiency is of current interest especially in high risk patients for reduced bone mineral density as in pediatric hematologic oncologic patients.
Methods
During a 4 year period 194 pediatric hematologic oncologic patients were screened for serological vitamin D deficiency (defined as 25 (OH)D levels <30 ng/ml and accordingly <75 nmol/l). 61 patients were in the prospective group 1 defined as screening at time of diagnosis, 35 patients were in the group 2 defined as screening at time of follow up <1 year after therapy and 98 patients were in group 3 defined as screening at time of follow up >1 year after therapy.
Results
Overall 112/194 patients (57.7%) had vitamin D deficiency, 49/61patients (80%) in group 1, 19/35 patients (54%) in group 2, 44/98 patients (44.8%) in group 3. All patients with proven vitamin D deficiency received an oral supplementation with cholecalciferol.
Conclusion
Screening for serological vitamin D deficiency is important to reduce the risk of reduced bone mineral density especially in patients at high risk as pediatric hematologic oncologic patients.
Disclosure
The authors declared no competing interests.
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P144

Hypomagnesaemia due to lead poisoning in the context of a heterozygous CLDN-16 mutation

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Background
3 year old boy born to non-consanguineous parents. He was diagnosed to have autism at 2 years of age. He had a history of pica.
Presenting problem
He was admitted with severe carpopedal spasms of hands and feet. Investigations revealed severe hypomagnesaemia at 0.26 (0.7–1.0) mmol/l, hypocalcaemia at 1.59 (2.2–2.6) mmol/l, hypokalaemia, hyponatremia and moderately low vitamin D levels. Parathyroid hormone concentration was low. Urine analysis revealed loss of sodium, calcium, magnesium and sodium. Renal functions and renal ultrasound were normal.
Clinical management
He received multiple intravenous infusions of sodium, potassium, calcium and magnesium and was started on oral calcium, magnesium and colecalciferol. Hypocalcaemia resolved within few days. Parathyroid hormone concentrations normalised on treatment with intravenous magnesium. However, hypomagnesaemia was severe and persistent despite treatment and renal magnesium losses continued. Meanwhile, blood film analysis revealed basophilic stippling of red blood cells suggestive of lead poisoning. Plasma lead concentration was extremely high and he received chelation therapy with dimercaptosuccinic acid, following which lead concentrations decreased. During chelation treatment, intravenous magnesium was switched to oral magnesium which could be gradually weaned and stopped after 10 weeks.
Genetic studies sent to assess known genetic causes of hypomagnesaemia revealed a previously described, but heterozygous mutation in CLDN16 gene. Heterozygous carriers are not usually symptomatic.
Discussion
Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC) is an autosomal recessive condition that is caused by homozygous mutations in the CLDN16 gene, which encodes claudin-16, an important tight junction protein expressed in Henle's loop and distal tubule of the kidney. FHHNC is characterised by excessive renal magnesium and calcium loss, persistent hypomagnesaemia, nephrocalcinosis and renal failure. The overall prognosis is poor, and definitive cure is by renal transplantation.
It is known that lead poisoning causes toxic effects to all organs, including the kidney, although magnesium loss has not been previously described in humans. In young rats, competitive antagonism between lead, calcium and magnesium has been shown in experimental studies. We suggest that, in our patient, lead poisoning resulted in hypermagnesuria in the context of a heterozygous CLDN16 mutation.
Disclosure
The authors declared no competing interests.
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P145

Zoledronate as first line therapy for pediatric osteogenesis imperfecta?

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Background
In pediatric osteogenesis imperfecta (OI), bisphosphonates (BPs) are considered the best treatment option to increase bone density and reduce fracture rate. Pamidronate (PAM) is regarded as standard care for moderate to severe OI. The most recent added BP is intravenous zoledronate (ZOL). ZOL has practical advances over PAM, however research on its efficacy and safety is scarce.
Objectives
To investigate the efficacy and safety of treatment with ZOL inDutch children.
Methods
Retrospective data-analysis of Dutch children with OI who received ZOL between 2009–2014. Bone densitometry scans (DXA), lumbar spine radiographs, biochemical measurements, fracture rate and side effects were documented to assess efficacy and safety. Results at baseline were compared to those after one year and thereafter. In addition, patients' experiences with ZOL were identified using a semi-structured interview.
Results
25 children (1.2–18.8 years of age) were treated and included. Follow-up data were available for 1 to 3.5 years of treatment. Zoledronate treatment was

associated with a significant increase of bone density on DXA scans ($P<0.01$) and decrease of fracture rate ($P<0.01$). Vertebral height increased significantly in all patients ($P=0.02$) but there were no significant changes in vertebral index and discus coefficient. Furthermore, there was a significant decrease in total serum alkaline phosphatase ($P=0.03$). Infusion related adverse events, mainly flu like symptoms, were reported by 36% of the participants. There were no clinical symptoms of hypocalcaemia following infusion. The majority of patients felt that ZOL had made a positive clinical difference and the reported quality of life (QOL) increased significantly ($P<0.01$).

Conclusion

This retrospective analysis of Dutch children with OI confirms the efficacy and safety of treatment with ZOL. No severe side effects were documented and patients self-reported QOL increased. Should Zoledronate be applied as the first line treatment in pediatric OI?

Disclosure

The authors declared no competing interests.

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P146

Hypovitaminosis D and factors associated in healthy children aged 2–14 years old in Mexico

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Objectives

To estimate the status of 25-hydroxyvitamin D in healthy Mexican children and to describe factors related to vitamin D deficiency.

Methods

A cross-sectional study was conducted in children 2–14 years old in Mexico City and Toluca Edo de Mexico. Trained interviewers applied a questionnaire including all relevant demographics, medical history, sun exposure, sunblock use and skin phototype. Morning fasting blood was collected in all subjects for estimation of 25-hydroxyvitamin D using Liquid Chromatography-Tandem Mass Spectrometry, and intact parathyroid hormone molecule by radioimmunoassay. Height and weight was obtained to determine body mass index.

Results

A total of 261 children were included in the study, 49.9% were girls ($n=129$). The sample was divided in preschool (2–5 years; 25.7%), school age (6 to 11 years; 58.4%) and adolescents (≧12 years; 16.0%). According to body mass index per age, 66.3% of the total sample was classified as normal, and 27.8% were overweight/obese. Levels of concentration of 25-hydroxyvitamin D showed an overall median of 26.13 ng/ml and parathyroid hormone of 25 pcg/ml. Vitamin D deficiency (<20 ng/ml) was found in 10% of the sample ($n=26$), insufficiency (20–29 ng/ml) in 60.9% ($n=159$) and sufficient levels (>30 ng/ml) in 29.1% ($n=76$) No correlation was found between 25-hydroxyvitamin D and parathyroid hormone as expected ($r=-0.12$, $R^2=0.014$, $P=0.06$). When analyzing possible risk factors for vitamin D deficiency, no statistical association was observed with duration of sun exposure, use of sunblock and skin phototype.

Conclusion

Only 10% of the assessed children in this sample were vitamin D deficient. This prevalence is low when comparing to similar studies reported in Mexico. The type of assay to determine the Vit-D levels might be in part an explanation for the different prevalence numbers, however environmental factors should be further evaluated closely in order to determine wich are the factors influencing the low levels of this vitamin in order to take action towards preventive measurements.

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Disclosure

The authors declared no competing interests.

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P147

A severe form of cerebral palsy as a risk factor for the development of secondary osteoporosis in children

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Objective

Investigate bone mineral density in children with cerebral palsy (CP) with special focus on severe forms of CP.

Methods

Investigation encompassed 23 children, both genders, between 6 and 17 years of age, with diagnosed cerebral palsy, who were hospitalized between January 1 and December 31, 2014. Bone mineral density (BMD) was established using Dual-energy x-ray Absorptiometry – DXA method, at L1–L4 lumbar vertebrae and at the femur neck, and BMD results were analyzed according to criteria by ISCD Pediatric Position Statement from 2008. Severity of motor function disorder was assessed using Gross Motor Function Classification Scale (GMFCS), which has five levels (I–V; level I is mild, level V is severe level of motor disorder). In statistical analysis, descriptive statistics, χ^2-test and Kruskal-Wallis test were used.

Results

From total number of subjects, 56.5% were boys and 43.5% girls, with average age of 13 ± 3.565 years. Osteoporosis had 52%, osteopenia had 21%, and normal BMD had 13% of subjects. There were 70% of subjects with a motor disorder level V according to GMFCS, 13% with level IV, 17% with level I (no subjects with motor disorder levels II and III). Comparing the categories of BMD disorders with the level of motor disorder according to GMFCS, obtained a statistically significant difference among the respondents ($P=0.004$): there were 83% of children with level V among the subjects who have osteoporosis and 60% of children with level V among the subjects with osteopenia. All children with a normal BMD were GMFCS level I. In children with the level I the average value of z-score of the spine was -0.3 and z-score of the hip was -0.4 while these values in children with level V were -2.0 ($P<0.05$).

Conclusion

Children with CP have a disorder of bone metabolism with increased susceptibility to bone fractures, especially those with severe CP (nonwalkers).

Disclosure

The authors declared no competing interests.

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P148

Prevalence of vertebral fractures in survivors of childhood acute lymphoblastic leukemia

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Improvements on the overall cure rates for childhood acute lymphoblastic leukemia (ALL) have allowed the cure of over 85% of treated patients. At least 70% of survivors of childhood ALL cancers have substantial morbidities as a result of their treatment. Long term musculoskeletal complications in this population are currently receiving increasing attention because of their negative impact on the quality of life and ability to perform appropriate activities. Our objective was to better define the clinical characteristics associated with vertebral fractures (VF) in survivors of childhood ALL. Our study, part of the PETALE project, draws its subjects from a pool of 350 French-Canadian ALL patients aged under 19 at diagnostic whom have been in remission for at least 5 years post-diagnostic.

The patients for this study ($n=150$) were recruited as part of the PETALE project at Sainte-Justine UHC: 59% are females; the mean age at diagnostic of 5.6 ± 4.2 years; mean age at recruitment of 22.3 ± 6.7 years; 59% of patients were classified as high risk at diagnosis; treatment duration was on average 26 ± 4.7 months and was finished 171.6 ± 70.6 months ago. Lateral thoraco-lumbar spine radiograph and LS BMD were assessed. VF was assessed according to the Genant method. Results show a VF prevalence of 18%. Participants with VF had a median age of 6 years old at ALL diagnosis (2–17). No significant difference was observed between patients with VF compared to those without for ($n=118$): dose of radiation; glucocorticoid cumulative dose; LS BMD z-score; back pain, and vitamin D status.

The mechanisms by which VF occur in survivors of childhood ALL remains an open question. We will next investigate association of VFs with rare and common genetic variants. This may lead to new interventions and insights into osteoporosis prevention.

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Disclosure

The authors declared no competing interests.

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P149

Trabecular bone density decreased during 6 year observation in girls with Turner syndrome, but was not associated with fracture history

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Objectives
Increased fracture risk and decreased bone mineral density (BMD) have been demonstrated by several studies in Turner syndrome (TS). Affected females have short stature and present with primary amenorrhea. Good densitometric predictor of fractures and longitudinal data on BMD development in childhood and adolescence are still lacking.
Patients and methods
Single tertiary care endocrinology center longitudinal study was performed. Peripheral quantitative CT (pQCT) scans at the forearm were performed in 33 girls with TS (median age 12.1 year, range 6.0–16.4 year) biannually for a period of 6 years. Trabecular volumetric BMD (vBMD) and cortical thickness were assessed at the 4 and 65% site, respectively. *z*-scores were calculated based on published references. The 6-year changes of both parameters were investigated in girls with TS with regard to reference data, the participant's age of first measurement and an interview based fracture history. All TS girls were treated with recombinant human growth hormone. Oral oestrogen substitution was given to 27 participants, while the remaining six had spontaneous puberty.
Results
There were seven girls with prevalent fractures while three girls sustained at least one fracture during the follow up. The mean 6-year decrease in trabecular vBMD *z*-scores was 1.0 ± 1.16 SDS ($P < 0.001$), with no association with the ages of the first pQCT assessment (95% CI of beta estimate: -0.19–0.17) of the TS participants. There was no difference in 6-year change in trabecular vBMD between girls with and without positive fracture history (mean *z*-scores -0.73 ± 0.81 and -1.08 ± 1.24; $P = 0.42$). We observed no significant 6-year changes in cortical thickness *z*-scores (-0.31 ± 0.94, $P = 0.09$) and no association of these changes with the ages of the first pQCT assessment (95% CI: -0.08–0.21). The fractured TS girls did not show different cortical thickness changes over 6 years of observation compared with the changes in non-fractured TS girls (mean *z*-score changes -0.15 ± 0.56 and -0.35 ± 1.03; $P = 0.55$).
Conclusions
This longitudinal vBMD study in TS girls demonstrates that trabecular vBMD decreases with age, which may be due to the hypogonadism, despite providing the girls with widely accepted oral oestrogen substitution. Nor trabecular vBMD neither cortical thickness seem to be suitable for fracture prediction in TS.
Grant support
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Disclosure
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P150

Impaired bone mineral density in adult survivors of childhood cancer: a literature review

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Objectives
impairment of bone mineral density (BMD) is a complication of childhood cancer treatment. A comprehensive review on the occurrence of impaired BMD in childhood cancer survivors (CCS), and which disease subgroups are at risk has never been pursued so far. The aim of this study was to summarize all knowledge on BMD status and associated determinants in long-term adult childhood cancer survivors (CCS) based on available literature.
Methods
an electronic literature search was performed using PubMed, Medline, Scopus and Web of Science databases. Papers were included if patients were survivors of childhood cancer (median age at diagnosis $\leq$18 years), were at least a median period of 5 years after cessation of therapy, and had a median age of $\geqq$18 years old at BMD measurement. Outcome measures were total body BMD (BMD_{TB}), lumbar spine BMD (BMD_{LS}) and hip BMD, including BMD of the femoral neck (BMD_{FN}) and total hip (BMD_{TH}).
Results
We found 30 studies including survivors of pediatric acute lymphoblastic leukaemia (ALL) (14 studies), (non)Hodgkins' lymphoma (HL/NHL), brain tumors, osteosarcoma or all types of cancer. The median age at follow-up ranged from 18.2 to 33.3 years, and median time since diagnosis ranged from 4.8 to 27.7 years. The majority of the studies (18 studies) used univariate statistical analysis to examine possible determinants of BMD. More than half (50–60%) of the studies that assessed the $BMD_{TB,}$ $BMD_{LS,}$ BMD_{FN} and BMD_{TH} found significantly lower BMD values in comparison with healthy peers. Total body BMD_{TB} scores < -1 were reported in 2.8–38%, and lumbar spine BMD_{LS} scores < -1 in 19.3–65% of the survivors. Lowest *z*-scores were found in osteosarcoma survivors (BMD_{TB}: -1.3 and BMD_{FN}: -1.98). Lower body weight at adult age (DXA) and treatment with cranial radiotherapy, glucocorticosteroids or chemotherapeutic agents during therapy for childhood cancer were most frequently identified as independent determinants.
Conclusion
This review of mainly cross-sectional studies suggest that long-term CCS are prone to BMD impairment, and lower body weight at adult age (DXA) and previous treatment with cranial radiotherapy, glucocorticosteroids or chemotherapeutic agents were most frequently identified as independent determinants. Prospective studies including large representative cohorts of survivors with long-term follow-up are required to accurately assess the occurrence of clinical significant impaired BMD, and its independent determinants in CCS.
Disclosure
The authors declared no competing interests.
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P151

Do children with mild to moderate osteogenesis imperfecta (OI) with abdominal muscle weakness have a higher incidence of pars defects? A physiotherapy pilot

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Objective
Osteogenesis imperfecta (OI) is most commonly caused by a defect in the genes that produce type I collagen. Clinical features include low bone mass, fractures and spinal abnormalities. Pars defects are abnormalities in the pars interarticularis of vertebrae. There is a higher incidence of pars defects in the lumbar spine in children with OI compared to the normal population. Abdominal muscle weakness and altered spinal postures are common presentations in the children assessed in a national regional OI service. We therefore hypothesised that children who present with weakness in their abdominal muscles have a higher incidence of pars defects in the lumbar spine.
Method
51 children were assessed by specialist physiotherapists in the OI clinic. The age range was 5–15 years and all had a clinical diagnosis of type 1 or type 4 OI. All were ambulatory with a brief assessment of motor function (BAMF) score of $\geqq$9. Abdominal strength was assessed by the child's ability to sit up from a lying position. Weakness was identified if the child needed to push through their arms to achieve a sitting position. Lateral spinal x-rays were formally reported for all children.
Results
Of the 51 children, 36 required the use of their arms to get into sitting from a lying position indicating weakness in their abdominal muscles. Of these, five had confirmed pars defects. Of the remaining 15, five also had confirmed pars defects.
Conclusion
Abdominal weakness was identified in 70% of the children studied. Only 14% of this group had pars defects on x-rays. The data from this sample did not demonstrate a higher incidence of pars defects in OI children with abdominal weakness. However, all ten children with pars defects presented with altered postures in sitting and/or standing. The assessment of abdominal weakness was limited as it only measured trunk flexion during one activity. It did not assess the strength of abdominals and other trunk muscles involved in postural stability. Development of a more objective assessment of truncal muscle strength is needed in order to investigate the relationship between weakness and pars defects in children with OI.
Disclosure
The authors declared no competing interests.
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P152

Syphilitic bone disease: a case report

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Background
Syphilis remains a great imitator of myriad of clinical diagnosis. Congenital syphilis, though still uncommon, is on the rise once again. Recognition of syphilitic bone disease and its potential impact on growth is important for long term prognosis. We describe our experience of managing a child with congenital syphilis and multisite osteolytic lesions.
Presenting problem
A 6 week-old girl presented with a swollen and painful elbow with reduced movement, but was systemically stable. She had pallor, hepatosplenomegaly, erythematous skin plaques, clear nasal discharge and bilateral conjunctivitis. Born normally, she had developed florid maculopapular erythematous rash with vesicles and bullae in her groins and face. Initial differential diagnoses included osteomyelitis, and severe immunodeficiency.
Her investigations revealed anaemia, neutrophilia, raised inflammatory markers, normal bone marrow cytology and hypergammaglobulinemia. TORCH (congenital infection) screen confirmed positive syphilis serology, and dark ground microscopy revealed spirochetes in the skin lesions. Whole body MR scan and x-rays showed lytic abnormalities within the right elbow and acromioclavicular joints. Subsequent skeletal survey showed diffuse metaphyseal lucency suggesting osteochondritis, increased diaphyseal density and striations, with periostitis. These changes are consistent with secondary syphilitic bone disease.
Clinical management
Child was treated with intravenous benzyl penicillin sodium 1 00,000 units/kg per day in four divided doses for 14 days in accordance with international guidelines. In the following weeks, there was dramatic clinical improvement, with normalisation of the haematological and biochemical parameters. Her syphilis serology progressively improved and was negative at 18 months. Repeat skeletal survey at this stage revealed entirely normal long bones with no residual focal abnormalities of the growth plate, focal sclerosis or limb length discrepancy.
Discussion
Congenital syphilis has a broad spectrum of presentation. Radiologically, infants may have signs of osteochondritis with a distinctive 'cat bite' appearance. While antenatal screening facilitates early detection and treatment of maternal syphilis, congenital syphilis can potentially have devastating bone sequelae such as Clutton joints and sabre tibia with impact on growth, if left untreated.
Conclusion
Our experience suggests that prompt recognition and early vigorous treatment of this condition can lead to complete resolution of syphilitic bone lesions, promoting normal growth and development.
Disclosure
The authors declared no competing interests.

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P153

In-vivo high-resolution peripheral quantitative computer tomography assessment of skeletal microstructure in children with osteogenesis imperfecta

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Objectives
The clinical assessment of bone mass in children with osteogenesis imperfecta (OI) is normally assessed by DXA. Further information about bone microarchitecture is obtained from bone biopsy which is invasive and requires anaesthetic. High-resolution peripheral quantitative computer tomography (HRpQCT) is an *in-vivo* imaging modality capable of assessing skeletal microstructure and integrity to a resolution of 80 μm. To date, no HRpQCT studies have included the assessment of children with severe OI.
Methods
We plan to assess skeletal microstructure of the ultradistal radii and tibiae (distal 9 mm) of 22 children with mild to severe OI using HRpQCT (Scanco Medical AG) and DXA in comparison with healthy controls. A further six bisphosphonate naive children with OI will undergo longitudinal microstructural assessment to determine *in vivo* changes in cortical and trabecular structure following bisphosphonate therapy. During scanning of OI patients an anti-gravity supportive sleeve will be used to prevent fracture.
Results
We scanned a boy with type I OI (15.17 years) who has received 8 years bisphosphonate treatment (6 years risedronate; 2 years pamidronate). We compared him with a healthy male control matched for height (OI 1.60 cm vs control 1.69 cm), BMI SDS (23.8 kg/m^2 vs 22.3 kg/m^2) and Tanner stage (TS3). Subtotal BA (1757 cm^2 vs 1553 cm^2) and subtotal BMC (1294.9 g vs 1195.4 g) were 12.3% and 7.9% greater respectively in our OI patient. Subtotal BMD was 4.34% lower in our OI patient. Radial cortical area (41.7 mm^2 vs 31.1 mm^2), cortical thickness (0.67 mm vs 0.51 mm) and cortical BMD (750 mg/cm^3 vs 719.6 mg/cm^3) were 29, 27 and 4% higher in our OI patient. In contrast, trabecular spacing (0.407 mm vs 0.464 mm), trabecular number (1.96$^{1/mm}$ vs 2.16$^{1/mm}$) and thickness (0.052 mm vs 0.055 mm) were 13, 10 and 2% lower in our patient with OI. Trabecular BMD was thus 16% lower (121.3 mg/cm^3 vs 143.5 mg/cm^3). The inhomogeneity of trabecular bone was 45.84% higher for our OI patient suggesting disruption in normal trabecular organisation.
Conclusion
It is well recognised that bisphosphonates improve total body BMD in OI patients. Although our work is preliminary, HRpQCT demonstrated clear differences in the microstructural organisation. Further work determining the impact of bisphosphonate therapy on skeletal integrity and biomechanics (including microfinite element analysis) is merited.
Disclosure
The authors declared no competing interests.

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P154

A longitudinal, prospective, long-term registry of patients with hypophosphatasia

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Objective
Hypophosphatasia (HPP) is a rare, inherited metabolic disease characterized by bone mineralization defects and osteomalacia, as well as systemic manifestations, including seizures, respiratory insufficiency, muscle weakness, nephrocalcinosis, and pain. The biochemical hallmark of HPP is low serum alkaline phosphatase, resulting from loss-of-function mutations in the gene encoding tissue non-specific alkaline phosphatase. HPP presents a broad spectrum of disease severity classically defined by age at onset of symptoms (perinatal/infantile, juvenile, adult, odontohypophosphatasia (isolated dental symptoms only), and 'benign' prenatal), with recognized overlap between, and range of severity within, these forms. The rarity of HPP combined with its variable expressivity presents considerable challenges in the diagnosis and understanding of the disease. Here we describe the design of an HPP Registry, which will enable better characterization and understanding of the epidemiology and clinical course of HPP through prospective collection of demographic and longitudinal clinical data.
Methods
This multinational, observational, prospective, long-term registry will enroll at least 500 patients, beginning with a 6-site pilot study to assess effectiveness of the protocol. Patients of any age with HPP will be included, except for those participating in an Alexion-sponsored clinical trial. Sites will conduct the study in accordance with local regulations. Patient data will be collected retrospectively at baseline and thereafter at intervals of at least every 6 months in the course of routine clinical care. The protocol details data to be collected, recognizing that not all requested data will be available at all sites; performance of new clinical procedures is not required. Chart review and patient-reported data will be assessed. Retrospective data collection will focus on patient demographics and HPP disease history, including dates of onset and diagnosis; family history; clinical manifestations; biochemical testing; and genotype, if available. Data from medical and laboratory assessments specific to HPP will be recorded. Standardized questionnaire instruments will be used to quantify patient-reported burden of disease, functional status/disability and quality of life.

Conclusion
The HPP registry will provide a comprehensive real-life longitudinal profile of patients with HPP, including demographics, diagnosis patterns, genotype-phenotype correlations, country-specific findings, and impact of HPP on activities of daily living and quality of life.
Disclosure
Funded by Alexion Pharmaceuticals. All authors are members of the HPP Registry Scientific Advisory Board.
Camille Bedrosian, Kenji P. Fujita, and Alex Cole are the employees of Alexion Pharmaceuticals Inc.
Priya Kishnani, Cheryl Rockman-Greenberg, Lothar Seefried, Etienne Mornet, Keiichi Ozono, and Wolfgang Högler have received honoraria from Alexion Pharmaceuticals Inc.
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P155

Hydroxylase (CYP27B1) deficiency presenting with marked hypotonia, growth failure, hypoventilation, pulmonary hypertension and a renal proximal tubulopathy

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Background
1α-hydroxylase is a mitochondrial P450 enzyme critical to the synthesis of active calcitriol from the pro-hormone 25(OH) D. Multiple different mutations in the CYP27B1 gene have been identified that abolish or reduce 1α-hydroxylase enzymatic activity resulting in vitamin D dependent rickets type 1. Children with 1α-hydroxylase deficiency present with a clinical picture of joint pain and deformity, hypotonia, muscle weakness, growth failure and sometimes hypocalcaemic seizures or fractures in early infancy. We report on a Black-African child with a typical presentation, although the unusual additional feature of renal proximal tubulopathy.
Presenting problem
Male infant was referred aged 12 months with faltering growth (length and weight measurements below 0.4th centile), hypotonia and delayed gross motor development. He had been breast fed until aged 9 months. His mother had taken vitamin supplements during pregnancy and the child was on a standard vitamin D preparation. On examination he was also noted to have a small chest, subcostal recession and a mild thoracolumbar scoliosis.
Investigation results were consistent with rickets: Calcium 1.78 mmol/l, Phosphate 0.68 mmol/l, Alkaline Phosphatase 1970 IU/l, Parathyroid hormone 49.5 pmol/l, yet 25(OH) D was 87.5 nmol/l. Renal function was normal. Skeletal radiographs revealed generally demineralised bones with coarse trabeculae and widespread periosteal reaction. Metacarpal and rib fractures and a thoracolumbar kyphoscoliosis were identified. He was noted to have a mild metabolic acidosis, generalised aminoaciduria and increased renal excretion of B2 Microglobulin. White cell cystine was normal. Plasma 1α,25-dihydroxyvitamin D3 levels were found to be inappropriately low (55.6 pmol/l).
Clinical management
He required high dose 1α-Hydroxycholecalciferol therapy (200 μ/kg per day) and calcium supplements over 4 months to normalise bone chemistry, initiate bone healing (evident radiologically), improve linear growth and significantly improve motor development. Progress was complicated by on-going feeding difficulties and mild hypoxaemia during sleep with associated pulmonary hypertension requiring low-flow O_2 therapy. His acidosis and aminoaciduria resolved entirely.
Discussion
We present a 12 months boy with severe 1α Hydroxylase (CYP27B1) deficiency associated with a reversible renal proximal tubulopathy and cardiopulmonary complications. The precise nature of action of 1α,25-dihydroxyvitamin D3 in proximal tubular cells is not well understood.
Disclosure
The authors declared no competing interests.
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P156

Children with coeliac disease on gluten free diet have normal bone mass, geometry and muscle mass

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Objective
To evaluate musculoskeletal development using pQCT in children with coeliac disease (CD) on gluten free diet (GFD) compared with age and gender matched healthy controls
Method
38 children (18 males) with CD on GFD for a duration of 3.6 years (0.6, 12.5) underwent pQCT at 4%, 38 and 66% tibial sites. Bloods were collected in CD children only. Results reported as median (range).
Result
Median TTG was 1.8 IU/l (0.1, 114) with 30/38 (79%)children with TTG < 8 IU/. Median Biagi score that verifies compliance to GFD was 3 (0.0, 4.0) with 32/35 (91.4%) scoring 3 and 4 (good compliance). Median 25-hydroxyvitamin D was 49.5 nmol/l (21, 82). 1/34 (2.9%) had 25-hydroxyvitamin D < 25 nnmol/l. All children had normal serum calcium, phosphate, PTH and thyroid function. A history of fracture was reported in 7/38 (18%) of CD and 5/38 (13.2%) of healthy controls.

	CD (*n*, 38)	**Controls** (*n*, 38)	***p* value**
Age (years)	10.3 (4.8, 14.8)	9.3 (4.9, 15.7)	0.56
Height *z*-score	−0.2 (−1.5, 2.3)	0.2 (−2.3, 2.4)	0.01
BMI *z*-score	0.1 (−1.9, 2.2)	0.4 (−3.1, 2.4)	0.41
Grip strength (height) *z*-score	0.7 (−1.4, 3.4)	1.1 (−2.0, 3.3)	0.23
4% tibia			
Volumetric BMD (mg/cm^3)	288.8 (208.8,421.5)	304.3 (228.6,419.4)	0.82
Trabecular BMD (mg/cm^3)	232.2 (153.9,437.8)	244 (109.2,420.9)	0.36
Bone area (mm^2)	735.5 (67,1315.8)	714.6 (318,1313.3)	0.40
38% tibia			
Cortical BMD (mg/cm^3)	1044 (974.1,1180.2)	1059.4 (989.6,1203.8)	0.37
Cortical area (mm^2)	154.3 (44.5,244)	158.8 (90.5,268.5)	0.37
66% tibia			
Cortical BMD (mg/cm^3)	1020.1 (903.6,1134.9)	1033.4 (979.6,1165.3)	0.07
Cortical area (mm^2)	204.1 (93.8,322.5)	203.8 (102.8,335.8)	0.85
Periosteal circumference (mm)	72.6 (54.7,90.8)	69.4 (55.7,91.6)	0.38
Endosteal circumference (mm)	55 (38.1,75.7)	49.8 (39.5,71.4)	0.32
Cortical thickness (mm)	2.7 (1.3,4.5)	2.8 (1.9,4.1)	0.43
Muscle density (mg/cm^3)	77.8 (72.1,82.4)	79.1 (73.1,84.1)	0.09
Muscle area (mm^2)	3872.3 (241.5,5543.3)	3400.3 (2190.8,5692.8)	0.56
Fat area (mm^2)	1695.1 (822.8,3125.8)	1675.6 (584.8,4184)	0.63
Bone/muscle area ratio (%)	5.5 (4.2,6.9)	5.8 (4.2,8.2)	0.08

In adjusted regression model (age, height *z*-score), there were no differences between CD and controls for bone area (95% CI: −341.1 to +204.6, $P=0.62$), muscle area (95% CI: −27.8 to +284.1, $P=0.97$), periosteal circumference (95% CI: −4.6 to +1.7, $P=0.37$), endosteal circumference (95% CI: −6.o to +1.8, $P=0.28$) and cortical thickness (95% CI: −0.1 to +0.4, $P=0.33$). There were no significant associations between pQCT bone parameters with TTG, Biagi score, 25-hydroxyvitamin D or calcium in CD.
Conclusion
This first novel report of bone mass and geometry using pQCT in a group of children with CD on GFD demonstrates normal volumetric BMD and bone geometry compared with healthy controls. Our data questions the need for routine bone surveillance in such children with CD. Bone assessment in children with CD at diagnosis and changes with GFD are now needed.
Disclosure
The authors declared no competing interests.
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Hypoxia inducible factor-1α directly induces the expression of receptor activator of nuclear factor-κB ligand in MLO-Y4 osteocytes

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Osteocytes may function as mechanotransducers by regulating local osteoclastogenesis. Reduced availability of oxygen, i.e. hypoxia could occur during disuse, bone development and fracture. Receptor activator of nuclear factor-κB ligand (RANKL) is an osteoblast/stromal cell derived essential factor for osteoclastogenesis. Hypoxia induced osteoclastogenesis *via* increased RANKL expression in osteoblasts was demonstrated. Hypoxic regulation of gene expression generally involves activation of the hypoxia-inducible factor (HIF) transcription pathway. In the present study, we investigated whether hypoxia regulates RANKL expression in murine osteocytes and HIF-1α mediates hypoxia-induced RANKL expression by transactivating RANKL promoter to elucidate the role of osteocyte in osteoclastogenesis in the context of hypoxic condition.
Expression levels of RANKL mRNA and protein as well as hypoxia inducible factor-1α (HIF-1α) protein significantly increased in hypoxic condition in MLO-Y4s. Constitutively active HIF-1α alone significantly increased the levels of RANKL expression in MLO-Y4s under normoxic conditions, whereas dominant negative HIF-1α blocked hypoxia-induced RANKL expression. To further explore if HIF-1α directly regulates RANKL transcription, a luciferase reporter assay was conducted. Hypoxia significantly increased RANKL promoter activity, whereas mutations of putative HIF-1α binding elements in RANKL promoter prevented this hypoxia-induced RANKL promoter activity in MLO-Y4s.
These results suggest that HIF-1α mediates hypoxia-induced up-regulation of RANKL expression and that in osteocytes in mechanically unloaded bone, hypoxia enhances osteoclastogenesis, at least in part, *via* an increased RANKL expression in osteocytes.
Disclosure
The authors declared no competing interests.

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P158

Extreme, biomechanically-explained remodelling of biological femoral reconstructions in pediatric oncology

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Introduction
Vascularised fibula autograft combined with a massive bone allograft (Capanna 2007) is used in skeletal reconstructions in children. If vascularisation is successful a clear remodelling of the reconstruction can be observed. This study aims to define a protocol to characterise bone's structural evolution in skeletal reconstructions through a computer-aided analysis, and attempts a biomechanical interpretation of the observed phenomena through a multiscale model. This was applied to a paradigmatic case (femoral reconstruction, 7 years follow-up without revision surgery) that showed dramatic remodelling.
Methods
Eight CT datasets of the child (8 years at operation for Ewing's sarcoma) during follow-up were available. The evolution of bone morphology, density and inertia moments was quantified. At the last control, a gait analysis was performed. Muscle and joint contact forces were calculated with personalised musculoskeletal model (Figure 1) (Valente 2014), and used as inputs to calculate bone and plate safety factors, and bone remodelling stimuli with a validated CT-based finite element model (Schileo 2014). Different screw-removal configurations to reduce the stress-shielding were simulated.
Results
The geometry and density of the allograft changed dramatically during follow-up, towards a reorientation of the inertia tensor of the reconstruction to that of the contralateral femur. The overall safety of the reconstruction was not challenged (safety factor ≥ 3). However further bone resorption is foreseen because extremely low values of the bone remodelling stimuli were found. Only a complete removal of the proximal screws could restore a physiological, contralateral-like bone strain configuration.

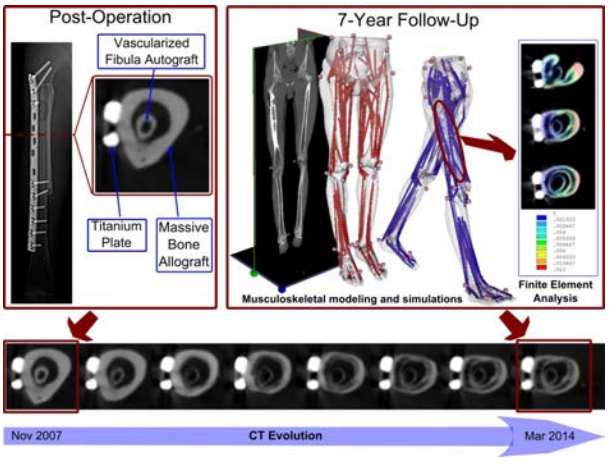

Figure 1

Conclusion
We successfully quantified load-induced bone remodelling. The extreme remodelling pattern was explained by the multiscale biomechanical model, which raised concerns for the long-term adaptation.
References
Capanna, *Orthop Clin North Am.* 2007.
Schileo, *J Biomech* 2014.
Valente, *Plos One* 2014.
Disclosure
The authors declared no competing interests.

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The usefulness of bioelectrical impedance analysis in the proper assessment of nutritional status in children and adolescents with idiopathic scoliosis

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Background
Based on our recent data, nutritional status disturbances (both under- and overweight) can be associated with the severity of scoliotic curve. Objectives: The study objective was to compare two methods for the assessment of nutritional status (routine BMI calculation vs body composition analysis by bioelectrical impedance analyzer (BIA)) in the group of pediatric patients with idiopathic scoliosis (IS).
Methods
317 patients (240 girls/77 boys) in mean age of 14.11 ± 2.79 years, with IS were qualified into the study. Scoliotic curve was assessed by Cobb's angle and angle vertebra rotation (AVR). Height, weight, waist and hip circumferences were measured and BMI, BMI *z*-score, waist/height ratio (WHtR) and waist/hip ratio (WHR) were calculated in the entire group. Body composition parameters as: fat mass (FAT), fat-free mass (FMM), predicted muscle mass (PMM) and total body water (TBW) were evaluated using bioelectrical impedance analyzer. Nutritional status was classified by centile charts for BMI as underweight, normal weight, overweight, obesity and for FAT% as underfat, lean, overfat, adiposity.
Results
Nutritional status assessed by BMI has been associated with the 21.1% of misclassification, comparing with BIA. There were important differences between percent of underweight vs underfat patients (13.9% vs 9.5% respectively), overweight vs overfat (5.4% vs 7.9% respectively) and obesity vs adiposity (2.8% vs 5.0% respectively). There was no significant correlation between BMI and scoliosis severity in the subgroups classified by standard measurement. However BMI *z*-score correlated significantly with either, Cobb's angle and AVR in every BMI classified subgroups. There were also significant correlation between body composition parameters (BIA) and vertebral deformity only in the normal BMI group. After the correction to the FAT%, finally 252 (78.9%) of children were properly classified, and in this group of IS patients

statistical analysis showed strong ($P<0.001$) significant correlation between either, Cobb's angle and AVR vs every (standard and bioelectrical) anthropometrical parameters.
Conclusions
i) Nutritional status classification by BMI assessment overestimates the underweight and lead to the underestimation of both overweight and obesity in patients with IS. ii) Bioelectrical impedance analysis is a useful tool for the proper nutritional status assessment in pediatric population with IS. iii) Properly assessed nutritional status is significantly associated with the severity of scoliotic curve assessed by Cobb's angle and AVR.
Disclosure
The authors declared no competing interests.
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Prevalence of muscle deficits in survivors of childhood acute lymphoblastic leukemia

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Overall cure rates for childhood acute lymphoblastic leukemia (ALL) have improved allowing the cure of over 85% of patients. At least 70% of survivors of childhood ALL cancers have substantial morbidities as a result of their treatment. There is evidence that survivors of ALL have increased rates of long-term skeletal muscle dysfunction and weakness. Our objective was to determine the percentage of patients with muscle dysfunctions (muscle force, power, endurance, and % of fitness impairment) and to define the clinical characteristics associated with muscle dysfunction in long-term ALL survivors. Our study, part of the PETALE project, draws its subjects from a pool of 350 French-Canadian ALL patients aged under 19 at diagnostic that have been in remission for at least 5 years post-diagnostic.
The patients for this study ($n=150$) were recruited as part of the PETALE project at Sainte-Justine UHC: 59% are females; the mean age at diagnostic of 5.6 ± 4.2 years; mean age at recruitment of 22.3 ± 6.7 years; 59% of patients were classified as high risk at diagnosis; treatment duration was on average 26 ± 4.7 months and was finished 171.6 ± 70.6 months ago. Study participants were assessed once by mechanography, bone mineral density (DXA) scans, 6 min walk tests, and pQCT scans. Results show a high prevalence (32%) of low muscle power (Pmax/body mass lower than -2 s.d.) compared to age- and gender-specific reference values. Significant differences were observed between patients with muscle dysfunction compared to those without for: the high-risk DFCI protocol prognosis group, exposure to radiation; BMI ($P<0.001$). One third of all participants are vitamin D deficient (<50 nmol/l) but without significant differences between low and normal muscle power groups.
Since this population mostly consists of young adults and adolescents, these data raise concerns on their future muscle and bone health.
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Disclosure
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P161

Unusual adverse reaction of pamidronate: thrombophlebitis

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Pamidronate, used for the treatment of paediatric osteoporosis, reduces the fracture rate and improves ambulatory status. Pamidronate is a potent inhibitor drug of bone resorption. After i.v. administration, the drug is extensively taken up in bone, where it binds with hydroxyapatite crystals in the bone matrix. Matrix-bound pamidronate inhibits osteoclast activity. Pamidronate is well tolerated by most patients.
We report a patient who developed venous thrombophlebitis after pamidronate treatment. Regimen for pamidronate infusion were 1 mg/kg per day for 3 days every 3–4 months. Adverse reaction was observed after second infusion. Evaluation associated with thromboembolitic event was normal. Third infusion was continued via different vein and there was no adverse reaction.
The history of venous thrombophlebitis may not be a formal contraindication to treatment with pamidronate, but the patient should be made aware of this possible complication before embarking on this form of treatment.
Disclosure
The authors declared no competing interests.
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Abstract withdrawn.

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Whole blood gene expression analysis in idiopathic infantile hypercalcemia due to compound heterozygous mutation in the *CYP24A1* gene in an Austrian 4-month-old boy and his family

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Defects in 24-hydroxylation caused by vitamin D-hydroxylase (*CYP24A1*) loss-of-function mutations lead to decreased degradation of $1,25(OH)_2D$ and the syndrome of idiopathic infantile hypercalcemia. Affected individuals show increased sensitivity to vitamin D and may develop severe hypercalcemia and hypercalciuria, even with small doses of vitamin D.
Presenting
The objective of the study was to investigate the gene expression profile in peripheral blood of a 4-month-old boy with a compound heterozygous *CYP24A1* mutation suffering from idiopathic infantile hypercalcemia in contrast to his family members and to healthy controls.
A 4-month-old boy was first diagnosed with hypercalcemia, highly increased 25-hydroxyvitamin D (25(OH)D) levels, and symptoms of acute renal failure at the Department for Pediatrics and Adolescent Medicine including dehydration, lethargy and reported problems in gaining weight.
A compound heterozygous mutation of *p.R396W* und *p.R439C* was identified in the *CYP24A1* gene. Whole blood gene expression analysis was used for the first time to identify changes in the mRNA profile of relevant calcium and vitamin D metabolism genes, depending on the mutation status in the patient and the family members compared to healthy controls. Therefore, RNA was isolated from whole blood samples using the PAXgene RNA system (BD, PreAnalytix). We were able to show significantly decreased gene expressions for the *CYP24A1* gene in the mother and the patient as well as decreased expressions of the calcium sensing receptor (*CASR*) in the brother, father and the infant. Significantly decreased *CYP27A1* as well as vitamin D receptor (VDR) expressions were found only in peripheral blood from the patient in contrast to his family members and to healthy controls.
Heterozygous *CYP24A1* mutations might cause different clinical symptoms depending on the gene expression status. Although the mother and brother showed the same *p.R396W*, and the father the same *p.R439C CYP24A1* mutation, only the patient developed severe symptoms. A classic vitamin D intoxication has been characterized in the infant with significantly decreased *VDR* as well as *CYP27A1* gene expressions. In parallel to DNA and potential epigenetic diagnostics, RNA expression from whole blood could help to characterize specific changes in these patients.
Disclosure
The authors declared no competing interests.
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P164

Effect of vitamin D supplementation on glucose metabolism, immune function and bone turnover in children with vitamin D deficiency

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Objectives
To assess the effects of short-term vitamin D supplementation on bone metabolism, glycaemic status and immune function in vitamin D deficient children.
Method
Treatment with daily 5000 IU cholecalciferol supplementation for 6 weeks. At baseline and end of treatment serum 25 hydroxyvitamin D (25(OH)D), parathyroid hormone (PTH), alkaline phosphatase (ALP), serum collagen type 1 cross-linked C-telopeptide (CTX), serum calcium, HbA1c, sex hormone-binding globulin (SHBG), fasting insulin, fasting blood glucose, and homeostasis model assessment index–estimated insulin resistance (HOMA-IR) were measured. Leukocyte subsets analysis was performed for (T/B cells) and T regulatory cells. Fifteen different cytokines/chemokine (IL2, IL4, IL5, IL6, IL8, IL10, IL12, IL17, EOTAXIN, MIP-1b, IP-10, TNFα, INFγ, RANTES, and MCP1) were measured.
Results
25 children enrolled in the study with median (range) age 5 years (10 months, 9.5 years). Serum 25(OH)D concentration increased from 29 (14, 125) mmol/l to 115 (37, 225) mmol/l at 6 weeks, $P<0.0001$. Serum PTH concentration decreased from 5.5 (3.6, 134) pmol/l to 3.9 (1.9, 6.8) pmol/l at 6 weeks, $P<0.0001$. In 17 patients whose glucose, insulin and HOMA-IR data were measured, serum 25(OH)D increased significantly from 27 (14, 125) mmol/l to 110 (37, 225) mmol/l, $P<0.001$. HOMA-IR fell from 1.84 (0.16, 20.29) to 1.59 (0.07, 12.5) and insulin secretion decreased from 11.1 (2.46, 99.2) μIU/ml to 8.1 (1.8, 66.6) μIU/ml. However, this reduction was not statistically significant ($P=0.5$ and $P=0.5$ respectively). There was a significant correlation between fasting insulin and both PTH and alkaline phosphatase at base line ($r=-0.6$, $P=0.0009$ and $r=-0.5$, $P=0.02$ respectively). No changes were observed in glucose, HbA1c and SHBG. Nineteen patients had sufficient blood available for cytokine assay and eight patients underwent flow cytometry for leukocyte subsets (T/B cells) and T regulatory cells with no significant change over time.
Conclusion
Supplementation of daily 5000 IU cholecalciferol has a significant effect in markers of bone turnover. PTH but not vitamin D level at baseline was found to be significantly associated with fasting insulin levels. There was no evidence of an effect of treatment with vitamin D on immune function.
Disclosure
The authors declared no competing interests.

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P165

Clinical masks of the tricho-rhino-phalangeal syndrome: based on the series of four cases from Poland

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Background
Tricho-rhino-pharyngeal syndrome (TRPS) is a rare genetic disorder, which is characterized by craniofacial and skeletal abnormalities. Presenting problem: This report presents four cases of TRPS (three sporadic and one familial). Clinical presentation included typical facial features (pear-shape nose, long flat philtrum, thin upper vermilion border, and protruding ears), thin, sparse scalp hair, and different skeletal abnormalities with normal mentation. All of them were admitted to the Department of Paediatric Endocrinology due to different endocrinopathies suspicion.
Clinical management
Case 1: a 5.5-year-old boy with short stature (GH deficiency excluded), clinically no skeletal abnormalities, but radiological assessment confirmed cone-shaped epiphyses at the phalanges. Moreover his father manifested the typical disease phenotype (not genetically confirmed yet). Case 2: a 12-year-old girl hospitalized with growth velocity retardation, with clinical and radiological epiphyseal deformities in phalanges, right humerus, and brachydactyly of toes sent as a suspicion of the calcium and phosphorus metabolism disorder. Case 3: a 13.5-year-old with short stature (GH deficiency excluded), typical epiphyseal deformities in phalanges and Perthes-like left hip deformation. Interestingly, none of TRPS features were found in her twin sister. Case 4: a 11-year-old girl with the suspicion of Turner syndrome (excluded by normal karyotype), with short stature, mild deformities of phalanges. Moreover, in the medical history an orthopaedic surgery in both hips due to Perthes deformation was noted. Hormonal analysis showed also partial GH deficiency and now recombinant GH therapy is considered. Every girls (cases 2, 3, and 4) had also mild vitamin D insufficiency. In cases 2 and 3 a genetic analysis revealed interstitial heterozygous microdeletion of 8q24 which confirmed TRPS.
Discussion
The wide variability in clinical expression of TRPS can mimic the other pathology (i.e. GH deficiency, other syndromic growth retardation, other calcium-phosphorus metabolism disturbances). The cooperation of multidisciplinary team seems to be essential in the proper management of these patients.
Disclosure
The authors declared no competing interests.

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P166

The role of AMPK pathway in mediating the effects of metformin on mesenchymal stem cell differentiation

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Introduction
Insulin sensitising agents are reported to have a diverse range of effects on bone with metformin exerting positive effects and thiazolidinediones (TZDs) exerting negative effects. 5'AMP-activated protein kinase (AMPK) plays a critical role in cellular energy homeostasis. It is widely expressed in the body and can be activated by metformin.
Objective:
We investigated the role of AMPK pathway in mediating the effects of metformin on the differentiation of mesenchymal stem cells (MSCs) into osteoblasts and adipocytes.
Methods
Confluent murine MSCs (C3H10T1/2) were treated with 500 μM metformin and 100 μM A769662 (AMPK activator) respectively, in an adipogenic-inducing environment (the TZD, pioglitazone 10 μM) for 5 days. Cells were harvested and nuclear extracts prepared. Nuclear extracts were separated by SDS-PAGE and immunoblotted with primary antibodies to peroxisome proliferator-activated receptor gamma (PPARγ; marker for adipogenesis) and Runt-related transcription factor 2 (Runx2; marker for osteogenesis). Immunoblots were scanned using a Licor fluorescent reader. Adipogenesis was also quantified histochemically by fixing with 10% formalin followed by staining neutral lipids with Oil red O.
Results
MSCs treated with pioglitazone for 5 days demonstrated marked adipogenic phenotype with accumulation of lipid-rich vacuoles that stained positively with Oil red O. Pioglitazone induced a significant ($P<0.01$) increase in PPARγ1 and PPARγ2 expression compared to diluent control, as determined by western blotting. In the presence of pioglitazone, metformin suppressed PPARγ expression ($P<0.001$) to basal diluent levels, as did the AMPK activator, A769662 ($P<0.01$), which suggests that metformin acts through the AMPK pathway, at least to a degree, to suppress adipogenesis in MSCs. Runx2 expression was unaffected by treatment with either metformin or A769662, suggesting that AMPK is not involved in the induction of osteogenesis in these cells.

Conclusion
Metformin appears to exert its bone protective effects on MSCs by reducing adipogenesis, through activation of AMPK signalling, with no direct effect on osteogenesis.
Disclosure
The authors declared no competing interests.
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P167

Muscle power and force are predictors of bone microarchitecture and strength in healthy children and adolescents measured by high resolution peripheral quantitative computed tomography and jumping mechanography

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Puberty is a time for the development of sexual dimorphism in bone and muscle. The aim of this study was to compare sex differences in bone and muscle variables using high-resolution peripheral QCT (HR-pQCT) and jumping mechanography (JM) in children and adolescents. We hypothesised that sex differences to muscle force and power (Fmax and Pmax) may explain differences in bone strength.
Total cross-sectional area and density (Tt.CSA and D100), cortical bone mineral and tissue density (Ct.BMD and Ct.TMD), area and porosity (Ct.Ar and Ct.Po), trabecular density, number and thickness (BV/TV, Tb.N, and Tb.Th) were measured by HR-pQCT at the 8% distal tibia. Fmax and Pmax were measured using JM. Sex differences were tested using multiple regression, adjusting for: sex, age, age^2, puberty, height, weight, Fmax and Pmax. Sex-by-puberty and sex-by-Fmax or Pmax interactions were tested. Data are presented as beta-coefficient (%) and *P*-value.
151 children (76 Females) aged 8–16 years were recruited. Fmax was associated with Ct.Ar, D100, BV/TV, Ct.Po, Tb.N and Tb.Th. Females had higher D100 (17%, $P<0.01$), Ct.BMD (11%, $P<0.001$), and Ct.TMD (5%, $P<0.05$) compared to males for a given Pmax, a difference that was greater at higher Pmax. Ct.Po (56%, $P<0.001$) and Tb.N (12%, $p<0.01$) were positively associated with Pmax in males, but not in females. Conversely, Tb.Th (17%, $P<0.01$) was positively associated with Pmax in females but not in males.
Our data suggest that sex differences in bone adaptation to Pmax during puberty exist. For a given Pmax, females accrue more bone than males. Pmax was positively associated with bone microarchitecture in males but not in females. This could be due to effects of oestrogen on mechano-sensitivity in the bones of females and testosterone-related increases in muscle function in males. These sex differences in bone adaptation may contribute to differences in bone phenotype and strength in adulthood.
Disclosure
The authors declared no competing interests.
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P168

Ambulatory impairment and bone status in subjects with Rett Syndrome: a 10-year longitudinal study

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Objective
Low bone mass is a frequent and early complication of subjects with Rett syndrome. As a consequence of the low bone mass Rett girls are at an increased risk of fragility fractures. The frequent occurrence of osteopenia raises questions regarding the direct influence of MECP2 gene mutations on bone growth and attainment of peak bone mass. It is well known that other critical factors such as the use of anticonvulsant drugs, the presence of scoliosis, the nutrition status, the low levels of 25OHD and the ambulatory impairment influence the attainment of peak bon mass in Rett subjects.
This study aimed to investigate the long-term influences of mobility on bone status in girls with Rett syndrome
Methods
In 47 girls with Rett syndrome, serum calcium, bone alkaline phosphatase, 25-hydroxyvitamin D and quantitative ultrasound (QUS) parameters at phalanxes by Bone Profiler-IGEA (amplitude dependent speed of sound: AD-SoS and bone transmission time (BTT)) were measured at baseline and after 5 and 10 years. The subjects were divided into two groups: non ambulatory ($n=22$) and ambulatory ($n=25$).
Results
At baseline both AD-SoS and BTT values were lower in non ambulatory with respect to ambulatory subjects, but the difference was not statistically significant. Non ambulatory subjects presented a significantly ($P<0.05$) later onset of age at menarche and lower birth weight with respect to the ambulatory subjects. BMI was significantly lower in non ambulatory subjects than in ambulatory subjects at each time point. At the 5-year follow up both ambulatory and non ambulatory Rett subjects presented a similar reduction in both AD-SoS and BTT. Also at 10-year follow up both non ambulatory and ambulatory subjects showed a significant reduction in AD-SoS (-4.7% $P<0.05$; and -3.4% $P=$n.s. respectively) and in BTT (-54% $P<0.05$; and -41% $P=0.05$ respectively) with respect to baseline.
Conclusion
In conclusion this longitudinal study suggests the usefulness of AD-SoS and BTT in the monitoring of bone status in Rett patients. In particular we found that QUS parameters are markedly decreased in non ambulatory subjects and that nutritional status play a key role in the progressive deterioration of bone status.
Disclosure
The authors declared no competing interests.
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P169

Comparison of the response to bisphosphonate treatment between acute lymphoblastic leukaemia and osteogenesis imperfecta type I

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Background
Osteoporosis in children with osteogenesis imperfecta (OI) type 1 and acute lymphoblastic leukaemia (ALL) is characterised by high bone turnover. However the ability of spontaneous healing and reshaping of bone is retained in ALL even in the absence of bisphosphonate (BP) therapy, but impaired in OI.
Aim
To compare the response to BP therapy in children with ALL and OI.
Methods
Retrospective case note review of children with ALL and OI type 1 (2008–2013) managed at a single tertiary centre. Clinical data and dual energy x-ray absorptiometry (DXA) results were collected at baseline and following first year of intravenous BP therapy.
Results
Ten patients (seven males) with ALL were compared to 12 patients (seven males) with OI type 1. Four of ten and 5/12 received zoledronic acid in ALL and OI respectively and the others received pamidronate. The median age at start of BP treatment for ALL and OI groups were (9.65 vs 10.27 years, $P=0.86$). The median height SDS of OI group was significantly lower compared to ALL group at the start of treatment (-1.38 vs 0.29, $P=0.001$). Growth during therapy (Δ height SDS) was not different between ALL and OI groups (-0.28 vs 0.045, $P=0.49$).
Compared to baseline, the lumbar spine bone mineral apparent density (LSBMAD) *z*-scores improved significantly in both groups (ALL: -2.45(range -3.6 to -0.90) to -0.45 (range -2.5 to 0.5), $P=0.005$; OI: -2.70 (range -4.20 to -0.29) to -1.1 (range -2.15 to 1.17), $P=0.003$)). The 1-year change in LSBMAD *z*-score during treatment was similar between groups (ALL 1.34 vs OI 1.64, $P=0.92$). However, at the end of 1 year of treatment the median LSBMAD *z*-score in ALL patients (-0.45) was not different from normal (zero), but that for OI was significantly lower than normal (-1.1, $P=0.010$).
Conclusion
LSBMAD improvement in ALL is comparable to that in children with type I OI. Although both groups responded similarly to BP treatment, LSBMAD was closer to normal in ALL patients after 1 year of therapy.
Disclosure
The authors declared no competing interests.
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P170

Reduced spinal volumetric trabecular bone mineral density in adolescent girls with anorexia nervosa

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Background
Anorexia nervosa (AN) presenting in childhood can have devastating implications for growth, puberty, menstruation and bone health. It may lead to altered bone structure and inadequate acquisition of bone mass with increased risk of fracture.
Objective
To describe growth, pubertal and bone mineral density data in a cohort of adolescents with AN managed in a tertiary metabolic bone service.
Methods
62 adolescent females with AN assessed between 2009 and 2014 underwent assessment of pubertal status, menstrual history, auxology and bone mineral density measured by DXA, QCT and pQCT. Size adjusted lumbar spine BMD (LS BMAD), LS volumetric (v) trabecular BMD (LS vTBMD), femoral neck BMD (FN BMAD), distal radial total & trabecular vBMD were measured at initial assessment.
Results
At presentation, the mean age was 16 years (1.45 S.D.). Seven had prepubertal onset of AN, 14 pubertal and 41 postpubertal. 25 were inpatient, 32% had back pain and one had experienced a metatarsal fracture from repetitive exercising. 42 presented with secondary amenorrhoea (mean duration 20 months, range 5–60). Mean BMISDS was −1.48 (−5.61–1.26). Baseline bone density *z*-scores are given in the table 1:

Table 1

	LS BMAD	LS vTBMD	FN BMAD	Distal radial total vBMD	Distal radial trabecular vBMD
z-score (S.D.)	−1.00 (0.96)	−2.01 (0.95)	−0.70 (0.98)	0.07 (1.25)	−0.09 (1.12)

LS BMAD *z*-score was ≤ -2.00 (−2.00 to −2.90) in 13 patients, whereas LS vTBMD *z*-score ≤ -2.00 (−2.04 to −4.18) in 29 patients. One had mild grade 1 vertebral endplate fractures of T_4, T_5 and T_7 on DXA vertebral fracture assessment. LS vTBMD was correlated with oestradiol concentrations and was significantly lower in those with oestradiol <120 pmol/l (−2.18 vs −1.70, $P<0.05$).
Conclusion
Adolescent girls with AN have reduced size adjusted BMD for age at the lumbar spine. The marked decline in LS vTBMD, possibly due to relative hypercortisolaemia (Misra, *Lancet Diabetes Endocrinology* 2014) may increase the risk of sustaining atraumatic vertebral fractures.
Disclosure
The authors declared no competing interests.

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P171

Bone-muscle unit assessment with pQCT in children with inflammatory bowel disease following treatment with Infliximab

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Objective
To evaluate bone and muscle mass in children with inflammatory bowel disease (IBD) following infliximab (IFX) therapy.
Methods
Prospective longitudinal study of 19 children (12 males), 17 crohn's disease (CD), 1 ulcerative colitis (UC), 1 IBD unclassified (IBDU) of bone evaluation commencing treatment with IFX. Bone and muscle parameters were measured by pQCT at the non-dominant distal radius at 4 and 66% at baseline and 6 months. pQCT parameters for area were adjusted for height. Results reported as median (range).
Results
At baseline 7/19 (37%)had moderate/severe disease activity whereas at 6 months this was 1/19 (5%). At baseline median ESR (mm/h) was23 (3.0, 70) whereas at 6 months this was 13 (4.0, 56) $P=0.09$. At baseline, median albumin (mg/dl) was 33 (17, 42) whereas at 6 months this was 37 (20, 44) $P=0.013$. Nine children (47%) who were on oral Prednisolone at baseline discontinued at 6 months. Seven children (37%) were not on oral Prednisolone at baseline and 6 months. One child (5%) who was not on oral Prednisolone at baseline was on Prednisolone at 6 months whereas two children were on oral Prednisolone at baseline and 6 months. Median volumetric BMD *z*-was −1.4 (−2.8, −0.4) at baseline and−1.4 (−2.8, −0.4) at 6 months ($P=0.64$). Median muscle area *z*-score were −1.8 (−4.3, −0.3) at baseline and −2.1 (−3.5, −0.5) and 6 months ($P=0.93$). Total alkaline phosphatase (UL) increased from 97 (37, 259) at baseline to 153 (29, 391) at 6 months ($P<0.0001$).In the seven children who were not on oral Prednisolone at baseline and 6 months, volumetric BMD *z*-score and muscle area *z*-score did not change. In the nine children who discontinued oral Prednisolone at 6 months, volumetric BMD *z*-score and muscle area *z*-score also did not change. In six children who did not progress in puberty, volumetric BMD *z*-score and muscle area *z*-score did not change. In the 12 children who showed progression in puberty, volumetric BMD *z*-and muscle area *z*-score also did not change.

Table 1

	Baseline	6 months	*P* value
Age (years)	14.8 (10.4,17.2)	15.3 (11.8,17.6)	
Height SDS	−0.7 (−3.6,1.8)	−0.7 (−3.7,1.8)	0.75
Weight SDS	−0.4 (−3.7,3.1)	−0.2 (−2.7,2.8)	0.42
Prepubertal	2/19 (11%)	0/19 (0%)	
Early/mid puberty	9/19 (47%)	7/19 (37%)	
Late puberty	8/19 (42%)	12/19 (63%)	
Paediatric Crohn's Disease Activity Index	27.5 (0,57.5)	5.0 (0, 32.5)	< 0.0001
Oral Prednisolone	10/19 (52%)	3/19 (16%)	0.04

Conclusion
In this preliminary report, despite improvement in disease activity, reduction in oral steroid, progression in puberty and increase in plasma UL following therapy with IFX, muscle bone assessment using pQCT in children with IBD over the short period did not show improvement.
Disclosure
The authors declared no competing interests.

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P172

The possibilities of bone regeneration in children

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Introduction
Using the autograft bones in treatment orthopaedic diseases and trauma is common. However, cases of the large bone fragments autoplasty in acute trauma is rare. We have studied the case of succesfull autoplasty of the large tibial fragment in severe road accident.
Materials and methods
Child O., born in 2000, was delivered to the emergency room of Mogilev City Hospital after road accident (he was hit by a car while crossing the street). His condition was serious. Besides other damage he had open fractures of the tibial and fibular bones in the lower-medial third with large defect of the tibia. Fragment of the tibia about 15 cm in length was found on the street by a driver and was delivered to the hospital. Debridment of the open fracture, tibial fragment autoplasty and ostheosyntesis with Ilizarov system were performed. Wound healed by secondary intention with partial marginal necrosis. Intensive antibioticotherapy was performed. The patient was discharged for outpatient treatment after 1 month. Ilizarov system was removed 4.5 months after trauma.
Results and discussion.
Patient has been examined 2 years after trauma. He has no complaints, gait is correct, no limping. Legs are the same length, no deformations. Slightly hypertrophic scar is on the anterior surface of the shin. Complete fracture healing, distal tibial physis closure and synostosis of the distal tibial and fibular bones are on the radiographs. Dystal tibial physis closure is on the opposite side.

Significance
This case shows the possibility of bone structure and extremities functions full recovering in severe trauma, which is accompanied by extensive soft tissue and large bone defects.
Disclosure
The authors declared no competing interests.
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P173

Papilledema in a toddler: An atypical presentation of X-linked hypophosphatemic rickets

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Background
X-linked hypophosphatemic rickets (XLH), the most common inherited rachitic disorder, is often misdiagnosed as nutritional rickets or physiologic bowing. Patients typically present in early childhood with progressive bowing deformities of the lower extremities and short stature, however may also develop craniosynostosis. Here we present a case of an adopted Caucasian male whose presentation of papilledema, craniosynostosis and hypophosphatemia eventually led to the correct diagnosis of XLH.
Presenting problem
Patient presented at 2 years of age with new onset esotropia following a minor fall. Fundoscopic exam revealed bilateral papilledema, evident on MRI and confirmed *via* elevated lumbar puncture opening pressure. Treatment with acetazolamide was initiated. Further past history revealed progressive lower extremity bowing and waddling gait for which he was evaluated by orthopaedics and started on vitamin D supplementation. Endocrine referral was made for frontal bossing, genuvarum deformity, widened wrists, and pectus carinatum.
Clinical management
Imaging confirmed diagnosis of rickets (widened and frayed long bone physes, premature fusion of sagittal sinus). Labs obtained while on acetazolamide and vitamin D showed normal calcium (8.8 mg/dl), low vitamin D (22.2 ng/dl) and phosphorus (2.6 mg/dl), elevated alkaline phosphatase (819 U/l), and parathyroid hormone (112 pg/ml). TRP/GFR was low at 65%.
Despite correction of vitamin D insufficiency, serum phosphorus remained low with urinary phosphate loss and worsening rickets on x-ray. Acetazolamide, known to cause phosphate wasting and metabolic acidosis, potentially exacerbated the patient's bony abnormalities; however further investigation revealed inappropriately elevated FGF23 (199 RU/ml). Genetic testing identified a PHEX mutation consistent with XLH. Papilledema failed to resolve necessitating surgical intervention. He was then weaned off acetazolamide, maintained on phosphorus and calcitriol supplementation, and is now showing signs of radiographic healing of rickets.
Discussion
XLH is often associated with sagittal synostosis[1] however there is only one case report[2] of a child with XLH and papilledema requiring surgical intervention. Here we report a case where significant papilledema was present initially, and diagnosis of XLH was confounded by history of suspected nutritional rickets as well as concomitant use of a medication causing renal phosphate wasting. It is important for general paediatricians and subspecialists alike to recognize rare causes of rickets, especially when the presentation is atypical.
1. Currarino G. Sagittal synostosis in X-linked hypophosphatemic rickets and related diseases. *Pediatr Radiol* 2007 **37**:805–812.
2. Glass L. Papilledema in the setting of X-linked hypophosphatemic rickets with craniosynostosis. *Case Rep Ophthalmol* 2011 **2**(3):376-81.
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P174

Case report of reversible cardiomyopathy secondary to 1 alpha hydroxylase deficiency

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Background
Dilated cardiomyopathy is the leading cardiac cause of death in children. Treatment options include heart transplantation. Reversible causes are rare but hypocalcaemia secondary to vitamin D deficiency is a recognised cause and presents during infancy in at risk populations. Risk factors include babies who were breast fed, dark skinned and from mothers with vitamin D deficiency. We present an unusual case of vitamin D replete, hypocalcaemic cardiomyopathy secondary to 1 α hydroxylase deficiency, which has not previously been described.
Presenting problem
A 4 month-old baby, born to consanguineous parents of Indian origin, presented acutely with poor feeding and shortness of breath. Chest x-ray showed an enlarged cardiac shadow and severe skeletal changes suggestive of rickets. He was found have dilated cardiomyopathy with severely compromised systolic function and left ventricular ejection fraction of 25%. He proceeded to have two hypocalcaemia seizures and bloods showed a low plasma corrected calcium level of 1.4 mmol/l, phosphate of 1.7 mmol/l, magnesium of 0.7 mmol/l and elevated PTH of 83.5 pmol/l. Although his mother had low vitamin D of 38 nmol/l, he had a normal vitamin D level of 96 nmol/l and had not been breast fed but given infant formula since birth.
Clinical management
The baby was commenced on intravenous calcium supplementation, oral phosphate, magnesium, oral cholecalciferol and alfacalcidol. Shortly after treatment was initiated, serum 25 vitamin D levels were 199 nmol/l with paired 1.25 vitamin D levels being inappropriately low at 43 pmol/l (48–145) suggesting a diagnosis of 1.25 hydroxylase deficiency. After doubling the dose of alfacalcidol, the intravenous calcium requirement could be reduced and finally discontinued 4 weeks after presentation. This child's dilated cardiomyopathy was managed with diuretics, digoxin and capropril. Although initially the child was considered for transplantation, the left ventricular dysfunction resolved and on discharge the left ventricular shortening fraction was 30%, within normal limits.
Discussion
Reversible causes of dilated cardiomyopathy are important to diagnose. Although vitamin D deficiency is the commonest during infancy, other causes of hypocalcaemia may also adversely affect cardiac function and must be considered. We present an unusual case of reversible hypocalcaemic dilated cardiomyopathy secondary to 1 α-hydroxylase deficiency.
Disclosure
The authors declared no competing interests.
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Effect of baseline vitamin D status on serum 25(OH) D level and body composition in breastfed infants on vitamin D supplementation

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Objectives
Vitamin D intake at a dose 400 IU/d is recommended for breastfed infants and is considered as sufficient. Vitamin D status is connected with bone mass and fat mass. We aimed to assess, if 400 IU/d has the same efficiency and impact on body composition in infants with different vitamin D status at birth (<20 ng/ml vs $\geqq 20$ ng/ml).
Methods
148 breastfed infants were supplemented with 400 IU/d of cholecalciferol up to 6 months of age. Serum 25(OH)D, iPTH and dual-x-ray absorptiometry (Lunar, Prodigy) were performed after birth and 3, and 6 months later. Participants were divided according to cord blood 25(OH) D level (group 1: 25(OH) D <20 ng/ml, group 2: 25(OH) D $\geqq 20$ ng/ml) (Table 1).
Results
A total of 124 (83.8%) infants completed the study. 25(OH) D level and compliance were similar in the study groups at 3 and 6 months. The prevalence of 25(OH) D level $\geqq 20$ ng/ml (94% vs 100%) and >30 ng/ml (64% vs 59%) were similar in both study groups after 6 months of vitamin D supplementation, respectively. The higher increment in 25(OH) D level was associated with the higher percentage change in bone mass, fat mass and length in vitamin D deficient infants between baseline and 6 months of age (Table 1).

Table 1 Comparison of serum 25(OH) D level and percentage change (%) of serum 25(OH) D level, iPTH, body composition (BMD – bone mineral density, FM – total fat mass, LBM – total lean body mass) and anthropometric parameters between study groups during 6 months of vitamin D supplementation. Data are presented as mean ± S.D. *P*-value < 0.05 are statistically significant.

Parameters	Group 1 ($n=78$) Cord blood 25 (OH) D <20 ng/ml	Group 2 ($n=46$) Cord blood 25 (OH) D ≧20 ng/ml	*P* value
25 (OH) D (ng/ml)			
Cord blood	11.5 ± 4.2	27.6 ± 5	0.0001
3 months	33.8 ± 7.8	34.7 ± 7.7	> 0.05
6 months	32.2 ± 7	34.6 ± 9.2	> 0.05
Increment in 25(OH)D (ng/ml)	20.7 ± 8.7	6.7 ± 9.5	0.0001
25(OH)D % change (%)	227 ± 146	27 ± 36	0.0001
PTH % change (%)	410 ± 345	408 ± 301	> 0.05
BMD % change (%)	50.3 ± 9	43 ± 14	0.03
FM % change (%)	279 ± 122	221 ± 85	0.01
LBM % change (%)	74.7 ± 22	74.7 ± 19	> 0.05
Weight % change (%)	107 ± 32	97 ± 26	> 0.05
Length % change (%)	33 ± 11	29 ± 9	0.002

Conclusions
Vitamin D supplementation at a dose 400 IU/d allowed to achieve 25(OH) D level > 20 ng/ml even in infants with vitamin D deficiency at birth. Threefold higher increment in 25(OH) D level was associated with higher percentage change of bone and fat mass but not lean body mass in vitamin D deficient infants.
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Evaluation of fibroblast growth factor 23 in patients with hypophosphataemic rickets
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Objective
Hypophosphataemic rickets (HPR) is associated with high concentrations of fibroblast growth factor 23 (FGF23). Chronically elevated FGF23 may impact on cardiac function and the skeleton. There is little evidence on how FGF23 changes with time in HPR or how it is affected by treatment. The aim of this study was to evaluate changes in FGF23 concentrations over time in patients with HPR.
Methods
Retrospective data was collected from our Metabolic Bone Database. FGF23 was measured at diagnosis when possible ($n=3$) and thereafter at every clinic visit whilst on treatment. Ten patients aged 0–13 years were included. Patients were classified as mild or severe phenotype based on clinical features.
Results
Mean age at diagnosis was 5.5 years (female (6): male (4)). Renal function was normal in all patients. Mean alfacalcidol dose was 32.3 ng/kg per day and mean phosphate dose 30 mg/kg per day. 43 measurements of FGF23 were recorded. Mean FGF23 at diagnosis was 115 RU/ml (S.E.M. ± 7.69). Mean concentration on treatment was 240.3 RU/ml (±23.0). The severe forms ($n=5$) of HPR had a mean FGF23 of 221.3 (±23.8), alfacalcidol dose of 35.7 ng/kg per day (S.E.M. ± 1.4) and phosphate dose of 33.9 mg/kg per day (S.E.M. ± 3.7), with mean serum phosphate of 0.82 mmol/l (S.E.M. ± 0.04) (ref range 1.13–2.20). Those with the milder form ($n=5$) of HPR had a mean FGF23 of 242.3 (±37.8), alfacalcidol dose of 33.1 ng/kg per day (±1.4) and phosphate dose of 22.9 mg/kg per day (±2.0), with mean serum phosphate of 0.90 (±0.03). Mean pre-treatment phosphate concentration was 0.74 mmol/l ($n=2$). Although phosphate dose was significantly higher in the severe group ($P=0.01$), FGF23 concentrations were not significantly different between these two groups ($P=0.67$). There was no correlation between FGF23 and PTH concentration, dose of alfacalcidol or dose of phosphate.
Conclusion
HPR was associated with an increase in FGF23 after commencing treatment. No significant difference in FGF23 concentrations was noted between patients with mild and severe phenotype. Factors contributing to higher FGF23 post treatment remain unclear. Klotho, a membrane protein that affects FGF23 signalling, is being analysed in these patients. Novel strategies to optimize FGF23 concentrations while on conventional treatment are required in patients with HPR.
Disclosure
The authors declared no competing interests.
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Fractures in boys with Duchenne muscular dystrophy and their relationship to age
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Objective
A retrospective review of bone morbidity in a contemporary cohort of boys with Duchenne muscular dystrophy (DMD) currently managed in a Scottish tertiary neuromuscular centre.
Method
Clinical details and results of bone surveillance were obtained in 47 boys, aged 9 years (2–16). DXA bone mineral content (BMC) at total body (TB) and lumbar spine (LS) were adjusted for bone area. Fractures were classified based on radiological confirmation. Results are reported in median (range).
Result
At last follow-up, 39/47(82%) were on steroid therapy and 26 (55%) were ambulant. 5/10 (50%) of those over 14 had delayed puberty and all of these boys had testosterone therapy. All were treated with oral vitamin D (800–1000 units per day) and of 35 who had Vitamin D measured, 5 (14%) had a level < 25 nmol/l. 12 boys (26%) had sustained a total of 15 symptomatic fracture events. Of these 15, 12 (80%) were appendicular fractures (AF) and 3(20%) were vertebral fractures (VF). AF occurred at a median age of 6 years (2.5, 14) in 9 boys. The distribution of these 12 AF was 7 (58%) tibia/fibula, 3 (25%) femur and 2 (17%) humerus/radius/ulna. Mechanisms of injuries were 11 (92%) minor fall and 1(8%) while being lifted. Median length of steroid exposure was 4 years (0, 10). 7/9 boys (75%) were ambulant prior to fracture. 2/11 (18%) lost ambulation after fracture. 3/12 (21%) of AF (femoral, tibia, fibula) occurred in two boys under 3 years who were steroid naïve and ambulant. DXA and vitamin D level within 1 year of AF were available in 10/12 fracture episodes. Median TB BMC SDS was 0.1(−0.8, 1.0) and LS BMC SDS was −0.2 (−1.2, 1.0). Vitamin D level was <25 nmol/l in 2/10 (20%). VF occurred at a median age of 11 years (9, 13) in three boys. 2/3 boys were ambulant. Median length of steroid exposure was 6 years (5, 8). DXA within 1 year of VF showed TB BMC SDS 0.3 (−0.2, 1.1) and LS BMC SDS −0.1 (−0.6,0.8). None had vitamin D <25 nmol/l.
Conclusion
In boys with DMD, symptomatic VF occur in older children, with longer duration of steroid therapy. AF occurs in younger boys and can also present in very young, ambulant, steroid naïve boys. Coincidental severe vitamin D deficiency or reduced BMC were not common findings at a fracture event.
Disclosure
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The precision of partial image analysis of trabecular bone microarchitecture by high-resolution magnetic resonance imaging in people with childhood-onset bone abnormalities
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Background and objective
High-resolution magnetic resonance imaging (hrMRI) can assess trabecular bone microarchitecture but the number of image slices required for reliable assessment is unclear.

Methods
MRI was performed just below the growth plate of the proximal tibia from 20 healthy controls (all female; median age 21 years (range 18–35) and 10 cases (three mals: seven females; median age 19.5 years (range 16–48) with known bone abnormalities including osteogenesis imperfecta and other endocrinopathies using a 3T-MRI with a resolution of $0.3\times0.3\times0.3$ mm. Images were analysed using Matlab to generate the trabecular bone microarchitecture parameters, including apparent trabecular volume to total volume (appBV/TV), trabecular thickness (appTbTh), trabecular number (appTbN) and trabecular separation (appTbSp). The mean values obtained from 20 of the most central images (20 images) were compared to that for ten images, five images and one image from the centre of the total image set using linear regression analysis. Co-efficient of variations (CV) within subject and between subjects were compared for the total and partial image set and significance level analysed with Levene's test and Mann–Whitney *U*-test.
Results
The mean trabecular bone microarchitecture estimates from ten, five and one images were strongly and positively related to the estimates from 20 images for appBV/TV ($r=1.00$, $r=0.99$, $r=0.97$, all $P<0.001$), appTbTh ($r=1.00$, $r=0.99$, $r=0.97$, all $P<0.001$), appTbN ($r=1.00$, $r=1.00$, $r=0.98$, all $P<0.001$) and appTbSp ($r=1.00$, $r=0.99$, $r=0.98$, all $P<0.001$). The mean intra-subject CV (s.d.) for appBV/TV in healthy controls was 2.6% (1.1%) for 20 images, 3.0% (1.5%) for ten images and 3.1% (1.5%) for five images. Cases have higher mean appBV/TV CV (s.d.) at 3.7% (2.1%) for 20 images, 4.7% (3.0%) for ten images and 4.3% (3.1%) for five images; all $P>0.05$ when compared to that of controls. However, sub-analysis of the four cases with osteogenesis imperfecta, a more severe osteopathy, demonstrated even higher mean CV (s.d.) at 4.6% (2.7%) for 20 images, 7.1% (3.1%) for ten images and 5.9% (3.6%) for five images ($P=0.183$, $P<0.005$ and $P=0.157$ respectively).
Conclusions
These findings indicate that partial MRI sets can reliably represent a larger complete set of images when assessing trabecular bone microarchitecture parameters. However, in cases with severe abnormalities of bone health, a larger set of images may need to be analysed to improve precision.
Disclosure
The authors declared no competing interests.
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An atypical case of bone fragility and dysmorphism with an unusual and novel de novo COL1A1 mutation
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We report a male child presenting with antenatally diagnosed bilateral talipes equinovarus, short stature, bilateral cryptorchidism and poor weight gain; born at 39 weeks gestation (birth weight 2.56 kg) to non-consanguineous Caucasian parents. Facial dysmorphism included a prominent forehead, brachycephaly, shallow orbits, a high anterior hairline, a narrow nasal bridge and small mouth with a thin upper lip. He had white sclera and was short for height (−4.4 SDS) with a relatively large head circumference (−2.2 SDS). His dentition evolved with dental enamel hypoplasia.
Presentation
At 6 weeks of age, he had a right transverse femoral fracture, followed by two right tibial fractures after Ponseti casting for correction of talipes. Delayed gross motor development due to prolonged periods of casting and mild speech delay were noted at the time. His bones were presumed osteopenic due to limb disuse.
Treatment
Pamidronate therapy was commenced at age 14 months before further casting and tenotomies. However, a non-union of the tibial fracture (pseudoarthrosis) was noted after an initial cycle of bisphosphonates. Further splinting after further bisphosphonate therapy resolved talipes and motor development normalised.
Investigations
A skeletal survey confirmed generalised osteopenia, with lambdoid Wormian bones and normal vertebrae. Lumbar spine DXA scanning reported low bone mineral density. Bone biochemistry was normal including vitamin D and PTH. A transiliac bone biopsy demonstrated severe trabecular and moderate cortical osteopenia.
Array CGH found a small duplication variant of uncertain significance at Xp, with no obvious association to the child's phenotype. Sequence analysis found a novel *de novo* in-frame deletion of *COL1A1* in exon 2, causing deletion of one amino acid residue in the N-propeptide of the α-1 chain of collagen type I. No N-propeptide in-frame mutations are reported in the OI mutation database (https://oi.gene.le.ac.uk). However, triple helix domain in-frame deletions of *COL1A1*, although uncommon, have been reported in cases usually with a severe OI phenotype. Abnormalities in N-propeptide processing have been reported to cause an Ehlers-Danlos (EDS) type VII (exon 6 mutations) or an EDS/OI overlap syndrome (triple helical mutations in exon 6 or higher). Functional work looking at *COL1A1* expression in fibroblasts is currently being undertaken.
Disclosure
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Rare diseases of bones, joints and vessels study
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Background
There are currently 456 rare bone disease recorded within 40 groups. Within many of these diagnoses there is marked heterogeneity of severity and complications that is often not explained by current understanding of disease mechanisms. There is an urgent need to improve the care of these patients by developing novel diagnostic tests and therapies based on understanding sub-phenotypes within existing diagnostic groups.
Aim
To develop a national cohort of participants with rare disorders of bones, joints or blood vessels in the UK from which to increase understanding of disease mechanisms for sub- phenotyping.
Method
5-year prospective cohort study. Participants aged 0–100 years with clinical diagnosis of a rare disorder of bones, joints or blood vessels are recruited *via* the study website www.rudystudy.org. Participants complete online questionnaires for health-related quality of life, pain and function questionnaires every 6 months; for children these including PedsQL4.0, CHAQ, PedQL and Wong-Baker Facies. Further phenotyping including physical examinations, DXA scans and blood and urine tests are performed depending on individual projects.
Results
The secure open-source rare diseases of bones, joints and vessels study (RUDY) database is now online and includes features such as web based registration, dynamic consent and online assessment and two-way communication. These features have been tested by over 100 to date participants successfully with good feedback. Further, this has brought together specialist centres across the UK from both paediatric and adult services within a single clinical and academic network.
Conclusion
The RUDY database has delivered a novel approach to recruit and standardize assessment patients across the life-course with rare diseases. The platform offers opportunities for international collaboration and cohort based research.
Disclosure
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Short stature in osteogenesis imperfecta: consider alternative diagnoses
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Background
A 15 year old boy with antenatally diagnosed osteogenesis imperfecta (OI) was reviewed following concerns about poor linear growth, lack of pubertal

development and persistent deciduous teeth. He had a history of crush fractures of L1–L2 and previous intra-medullary rodding of his right femur and had been on oral bisphosphonates (Risedronate 70 mg once weekly). He was significantly short (height SDS −4.9), substantially below his genetic potential (target height range 9^{th}–25^{th} centiles) and obese (BMI 35.4 kg/m^2, +3.2 SDS). On examination he had clinical features consistent with OI including blue sclera, ligamentous laxity and dentinogenesis imperfecta with delayed secondary dentition. However, he also had generalised increased subcutaneous adiposity, a dorsal fat pad and pink abdominal striae. He appeared hypothyroid with sallow complexion, dry skin and bradycardia and was pre-pubertal (testicular volumes 3 ml bilaterally) leading to a clinical suspicion of hypopituitarism.

Clinical management

Hypopituitarism was confirmed on biochemical investigations with secondary hypothyroidism (fT_4 9.3 pmol/l, TSH 0.04 mU/l), low gonadotrophins (LH 0.6 U/l, FSH 2.9 U/l), testosterone (<0.5 nmol/l), IGF1 (<5 nmol/l) and peak growth hormone (GH) concentrations (0.05 mcg/l) on a primed arginine stimulation test (once hypothyroidism corrected with levothyroxine). He also had delayed bone age and a small anterior pituitary with ectopic posterior pituitary on MRI. Bone mineral density (BMD) around the time of GH initiation showed lumbar BMD −1.7 S.D. and total body BMD −1.5. Testosterone gel was introduced 18 months after GH to allow a longer period of growth. Height improved from −4.9 SDS at diagnosis of hypopituitarism to −1.6 SDS (164 cm) at 19 years (lower end of the predicted target centiles).

Discussion

Good growth response to GH was seen, despite late treatment. Hypothyroidism, GH deficiency and hypogonadism will have affected his BMD. The key learning point from this case is that OI alone may not explain significant short stature. In this case, clinical findings were suggestive of an additional diagnosis and it is important to consider the possibility of a second pathology in children with short stature out of keeping with the severity of OI.

Disclosure

The authors declared no competing interests.

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A case of moderate osteogenesis imperfecta with cerebral palsy spastic quadriplegia; an impossible combination, or is it?

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A 29 week pre-term female infant, Molly (not real name), was referred to our multi-disciplinary Metabolic Bone Disease Service at the age of 19 months, with a combined diagnosis of inherited osteogenesis imperfecta (OI) and cerebral palsy (CP) spastic quadriplegia, resulting from a intra-ventricular haemorrhage at 7 weeks-old.

Diagnosis of OI was confirmed at birth following fractures. Molly was treated with IV Pamidronate from the age of 6 weeks at a local paediatric centre but had limited intervention from local community professionals e.g. physiotherapy. Reports of poor compliance, non-attendance and poor physical outcome brought Molly to our door. Prior to our meeting of her we had low expectations for function and progress, and high expectation for possible tone related fractures, severe deformity, and difficulty in achieving a positive outcome for this child.

This case study describes Molly's journey within our service; highlighting the challenges with the combined diagnosis and the complex therapeutic strategies and collaborative multidisciplinary approach used to manage her clinical symptoms and facilitate her development in all areas.

Molly is now 4 years 8 months old, and along with 12 weekly IV Pamidronate with medical review, receives regular intervention from our wider team; i.e. physiotherapy and occupational therapy, specialist nurses, orthopaedic and spinal surgeons, social work and psychology. Molly attends mainstream primary school with support, and is independently mobile in a lightweight self- propelling wheelchair using both hands near to equally. Prior to her recent orthopaedic surgery, Molly could stand with minimal assistance, and has made a surprisingly encouraging start towards an independent life ahead of her. Who could have predicted this outcome? There is very little literature describing this combination of bone fragility and increased muscle tone in the body. Can we prevent one impacting too greatly on the other?

Disclosure

The authors declared no competing interests.

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Deficits of vitamin D are strongly associated with methotrexate treatment in patients with juvenile idiopathic arthritis

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Vitamin D deficiency has been reported in adult patients with autoimmune diseases including rheumatoid arthritis, however, the data in patients with juvenile idiopathic arthritis (JIA) are inconsistent. The aim of the study was to assess serum 25-hydroxyvitamin D (25(OH) D in children and adolescents with JIA, and to determine potential risk factors for vitamin D deficiency.

In this cross-sectional study, we evaluated 189 patients with JIA (113 girls, 76 boys) aged 3–17.7 years (mean 12.3±3.9), having been diagnosed with oligoarticular (49%), polyarticular (44%) or systemic (7%) manifestations of the disease. The therapies included glucocorticosteroid (GCS) and/or methotrexate (MTX) treatment. Clinical status, anthropometric measurements using standard methods, laboratory markers of inflammatory process (C-reactive protein level and ESR), serum 25(OH) D, calcium (Ca), phosphorus (PO4), and total alkaline phosphatase levels (ALP) were determined. Hypovitaminosis D was defined as serum 25(OH) D <20 ng/ml.

In the whole studied group, the mean 25(OH) D concentration was 16.26± 9.4 ng/ml. Severely reduced 25(OH) D levels (<20 ng/ml) were found in 127 individuals with JIA (67%) and were independent of the clinical subtypes of JIA, nor were associated with age, sex or inflammatory markers. The 25(OH) D level was linked to higher serum Ca, ALP whereas it negatively correlated with BMI ($r=-0.2$; $P=0.01$). Obese JIA children showed significantly reduced 25(OH) D concentration in comparison to normal-weight peers. There was no relationship between steroid use and vitamin D status, although GCS treatment and the dose were associated with lower serum Ca (($r=-0.23$), PO4 ($r=-0.27$) and decreased ALP (($r=-0.79$; all $P<0.01$). Patients on MTX treatment also demonstrated lower Ca levels than those without MTX (2.51±0.09 vs 2.48±0.1; $P=0.02$), and a significant negative correlation was found between MTX weekly dose and 25(OH) D ($r=-0.34$). When children were divided in two groups according to the cut-off 25(OH) D level, the vitamin D deficiency (<20 ng/ml) was associated with MTX medication. The dose-dependent differences in 25(OH) D levels and serum Ca were observed between MTX users and non-users (26.96±4.6 vs 11.44±6.4 ng/ml; 2.52 vs 2.48 respectively; $P<0.01$), without ALP response.

Majority of children with JIA have reduced 25(OH) D. The high prevalence of clinically apparent vitamin D deficiency suggests a need to standardize vitamin D intake in this population. Methotrexate is a significant risk factor for suboptimal vitamin D status, therefore, patients on MTX therapy may require a correction of vitamin D supplementation to maintain optimal 25(OH) D levels. Long-term studies are needed to investigate whether the supplementation would alleviate the negative effect of MTX on vitamin D in JIA.

Disclosure

The authors declared no competing interests.

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A subtrochanteric femoral stress fracture following bisphosphonate treatment in an adolescent girl

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Background

Bisphosphonates are increasingly used to treat disorders of low bone mineral density (BMD) in children and adolescents. Long-term bisphosphonate use in adults has been associated with and increased risk of atypical subtrochanteric and diaphyseal femoral fractures (AFFs). To date, bisphosphonate-related AFFs have not been reported in children or adolescents.

Presenting problem

A 16-year-old girl presented with a 3-week history of left thigh pain. Her past medical history was significant for idiopathic juvenile osteoporosis diagnosed at age 11 years after presenting with a 1-year history of back pain and thoracic compression fractures. A DXA scan at that time showed decreased BMD with a lumbar spine z-score −3.9 and total body less head z-score −2.0. An extensive workup including a vertebral biopsy and testing for COL1A1/1A2 mutations did

not reveal an etiology for her low BMD. She was treated with intravenous pamidronate over a 2-year period, receiving a cumulative dose of 12 mg/kg. During the treatment period she had partial reconstitution of her vertebral bodies and no additional fractures. At pamidronate discontinuation (age 14 years), her lumbar spine *z*-score had improved to −1.6 and total body less head to −0.6. Just prior to the onset of thigh pain at age 16, she had joined a cross-country team after several years of inactivity, and was running 3–4 miles 7 days per week. Plain films showed diffuse cortical thickening of the bilateral femoral diaphyses, and a localized periosteal reaction at the medial cortex of the proximal left femur. A technetium-99 bone scan showed focal tracer uptake in the medial aspect of the proximal left femur, consistent with a stress fracture.

Clinical management

The patient was treated with restricted weight-bearing and relative rest. She received physical therapy and was placed on a program of muscle strengthening and generalized conditioning. After a protracted 16-week course her pain improved and she was able to resume regular activities. Plain films obtained 8-months after her initial presentation with thigh pain showed resolution of the periosteal reaction.

Discussion

This adolescent's presentation with a femoral stress fracture following high-dose pamidronate treatment shares several features in common with AFFs, including subtrochanteric location, localized periosteal reaction, and generalized cortical thickening of the femoral diaphysis. However unlike bisphosphonate-associated AFFs in adults, which typically develop on the lateral tensile cortical surface, this patient's stress fracture occurred at the medial cortex. Thus, while suggestive, the contribution of bisphosphonate treatment to the development of this patient's stress fracture is not known. Nevertheless, practitioners should evaluate thigh pain in children and adolescents with a history of bisphosphonate treatment, and should include AFFs and other femoral stress fractures in the differential.

Disclosure

The authors declared no competing interests.

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The effect of iron chelators on bone health in patients with thalassemia

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Thalassemia (Thal) is a genetic disorder of hemoglobin synthesis. In its most severe form patients require chronic blood transfusions to sustain life leading to iron overload unless excess iron is removed by chelators. Deferasirox (DFX) and deferoxamine (DFO) are the two most common chelators. DFX has recently been shown to reduce osteoclast activity *in vitro*.

Objective

To explore the association between chelation therapy, bone density and vertebral fracture in a retrospective sample of patients with Thal.

Methods

Clinical charts were reviewed from patients with Thal who received care at UBCHO from 2001 to 2014. Abstracted variables included patient demographics, length of chelation, and iron burden. BMD scans were performed on one DXA (Hologic Discovery v12.6.1); full lateral spine scans were re-analyzed by one observer, and scored using the semi-quantitative assessment (Genant) for vertebral abnormalities (VA) and severity. Statistical analyses were performed using STATA, v9.2.

Results

107 patients (22.8±11.4 years, 50% male) had on average 3.8 scans over 48.7 months. 52% of subjects were chelated with DFO, 27% with DFX, 8% with DFX+DFO (Combo), 13% no chelation therapy. On average, patients PA spine aBMD *z*-score was -2.4±1.1, hip aBMD *z*-score: −1.5±1.2, and whole body aBMD *z*-score: −2.5±1.0. Low bone mass (BMD *z*-score ≤ −2.0) was more common in DFO and DSX (76, 72% respectively) than those not chelated (19% $P=0.001$). After controlling for age, gender, hypogonadism, time on chelation and age start chelation, there was a significant effect of chelation medications on PA aBMD (mixed effects linear model, $P=0.002$). Those subjects taking DFX had the highest BMD compared to DFO (adjusted 0.064 g/cm^2 higher, $P=0.003$). Time on chelation and hypogonadism were stronger predictors of hip BMD than chelator type. 61 patients had at least one VFA scan, of which 40% were abnormal. Incident VA were observed in 9 patients over an average of 6 years. No significant differences were observed in prevalence or number of VA by chelation group.

Conclusions

Results suggest that chelation with the oral drug DFX is associated with higher spine aBMD but not reduced VA in Thal. Further study is needed to determine the etiology of this potentially beneficial effect.

Disclosure

The authors declared no competing interests.

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P186

Cole-Carpenter syndrome

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Cole-Carpenter syndrome (OMIM 112240) is characterised by bone fragility, craniosynostosis, ocular proptosis, hydrocephalus and a distinctive facial appearance. Intelligence is reported to be normal. In 1986, Cole and Carpenter reported two unrelated infants with multiple fractures and deformities of bone, with a skeletal phenotype similar to severe osteogenesis imperfecta (OI). In addition, these patients also had proptosis, blue sclerae, hydrocephalus and a distinct facial gestalt. They were reported to be of normal intelligence. Radiologically, these patients had characteristic skeletal manifestations including craniosynostosis and deformities similar to severe progressive OI. Since the first description, there have only been a few other case reports of patients with a similar phenotype. Collagen studies performed in previously reported patients have been normal. The molecular basis of this syndrome has not been elucidated and the inheritance pattern is still unknown.

We report a 12-year old patient with Cole-Carpenter syndrome who has a homozygous c.118G>T mutation in exon 1 of the *CRTAP* gene. We describe the clinical features and correlate this with her molecular results. This is the first report towards elucidating the molecular basis of Cole-Carpenter syndrome. Mutations in *CRTAP* have been described in association with type 2 (perinatally lethal) and type 3 OI (severely-deforming bones with extreme short stature, scoliosis and dentinogenesis imperfecta). The majority of *CRTAP* mutations result in a functional null allele with a consequent absence or significant reduction in levels of the protein. The spectrum of phenotypes associated with CRTAP deficiency range from severely-deforming to lethal presentations.

This report provides an aetiological basis for Cole-Carpenter syndrome, with an autosomal recessive inheritance and also expands the phenotypic spectrum for patients with mutations in the *CRTAP* gene. It also raises the possibility that Cole-Carpenter syndrome is a variant of type 3 OI and was never a distinct, rare bone fragility syndrome and postulate that craniosynostosis may be an acquired phenomenon in type 3 OI, further strengthening this suggestion.

Disclosure

The authors declared no competing interests.

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P187

TBS increases over time in pre-teen girls

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Muscle and loading force application alters bone structure and increases bone mineral density (BMD), particularly during growth. However, bone micro-architectural texture, as assessed by the trabecular bone score (TBS), changes during growth is unknown. We hypothesized that TBS would be positively correlated with growth and higher in growing girls participating in regular physical exercise.

68 girls (mean age 12±0.3 years; BMI 18±2.8 kg/m^2) were recruited from two middle-schools in Madison, WI. Spine DXA scans were obtained at three time points, fall 2011, spring 2012 and spring 2013, using a GE Lunar iDXA with software v13.31. Lumbar spine TBS was determined using Med-Imaps custom software to calculate raw values that were subsequently adjusted for tissue thickness based on a normative population of European girls. Tanner staging was obtained by self-report coincident with each DXA scan.

Overall, the mean L1–L4 BMD increased 1.36 s.d. ($P<0.01$) over 18 months, 0.845 (±0.12) to 1.022 (±0.13) g/cm^2. Over the same interval, adjusted TBS

increased ($P<0.01$) 0.83 s.d. from 1.433 ($\pm$0.07) at baseline to 1.491 ($\pm$0.07) at month 18. These observations persisted ($P<0.01$) when limiting the sample to those categorized as Tanner stage 2 or 3 at baseline ($n=52$). This groug demonstrated a L1–L4 BMD increase 1.37 s.d. ($P<0.01$) over 18 months, 0.855 ($\pm$0.12) to 1.034 ($\pm$0.13) g/cm^2. Similarly, TBS increased ($P<0.01$) 0.94 s.d. from 1.437 ($\pm$0.07) at baseline to 1.495 ($\pm$0.07). No correlation was observed between TBS and BMD change at 18 months ($P>0.1$).
In conclusion, this first report of TBS in adolescent girls demonstrated BMD and TBS increases with age and Tanner stage, suggesting TBS may be of benefit in the assessment of pediatric bone health. The apparent greater increase in BMD vs TBS may suggest that bone microarchitecture has largely been established by age 12 and that the primary growth activity is bone mass/size accrual. Additionally, results may differ using groups with, longer follow-up or larger sample size. Further research documenting TBS changes during growth, and potential ways of optimizing skeletal structure in adolescents, is indicated.
Disclosure
Renaud Winzenrieth is Senior Scientist at Med-Imaps
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P188

Fractures, bone mass and geometry in black and white South African children: The Birth to Twenty cohort
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The prevalence of fractures in white children in South Africa is double that of black children (1). White males who fractured were shown to be more physically (2). The aim of this study was to compare the bone mass and geometry measures using peripheral quantitative computed tomography (pQCT) and dual energy x-ray absorptiometry (DXA) in black and white children with and without a history of fracture to determine the risk factors for fractures.
Lifetime fractures were recorded retrospectively in subjects from the Birth To Twenty cohort up to the age of 17 years. The findings of fracture and bone mass using DXA to those findings of fracture and bone geometry using pQCT were compared.
Outcome measures for DXA were total body less head bone area (TBLH BA), total body less head bone mineral content (TBLH BMC) and site-specific measurements of bone area (BA) and BMC at the radius (R), hip (H), hip neck (HN) and lumbar spine (LS). Outcome measures for pQCT were trabecular volumetric (v) BMD and total cross-sectional area (CSA) at the distal site (4%), and cortical vBMD, cortical CSA, total CSA and the polar stress-strain index (SSI) at the proximal site of each bone (38% tibia, 65% radius). Within groups stratified by sex and ethnicity, Mann–Whitney tests were used to compare measures between subjects who had fractured and those who had not.
White males who fractured have greater bone area and BMC, measured by DXA, but no associations were found among females or black males. White males who fractured had greater total CSA at the distal radius and at the proximal tibia. Black males who had fractured had lower trabecular vBMD at the distal radius than non-fracturing black males. Among females, no associations were found between any pQCT measure and fracture. Cortical CSA, cortical vBMD and SSI were not associated with fracture in any group.
In conclusion, fractures were associated with greater bone size at certain sites in white males as measured by both DXA and pQCT. Physical activity and other environmental factors might therefore be more important than bone structure in determining fracture risk in healthy children.
Disclosure
The authors declared no competing interests.
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P189

Two infants with the diagnosis of infantile hypophosphatasia: case report
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Hypophosphatasia is an autosomal recessive rare metabolic disorder characterized by decreased bone mineralization. It can be seen in infancy, childhood or adolescence. Disease occurs due to the loss of non-specific alkaline phosphatase activity in liver, kidney and bones. There is no specific treatment. Two infants with growth retardation and failure to thrive diagnosed as infantile hypophosphatasia are presented.
Our cases had abnormalities including short stature, failure to thrive short, bowed extremities, generalised hypotonia, a small funnel chest, soft calvaria, very large fontanel, extremely wide cranial sutures, high-arched palate, low-set ears and a depressed nasal bridge. Serum alkaline phosphatase activity was 55 U/l in a 4 month-old girl and 44 U/l in a 1-month old boy respectively (Normal: 145–420 U/l). Serum calcium concentrations were 10, 4 and 10.2 mg/dl respectively (Normal: 8.9–10.3 mg/dl). Urine test for the presence of phosphoethanolamine was able to evaluated in case 2 which revealed 30 μmol/mmol of creatinine (normal child; <25 μmole/mmol creatinine).
Radiographs showed hypomineralisation of all bones, especially the calvarium, long bones and ribs; widening of sutures; and poor ossification of the calvarium. Bowing was apparent in the distal portions of both upper and lower extremities.
In this article we described two unrelated patients having a condition that can be considered as likely severe type of hypophosphatasia with high mortality.
In conclusion, hypophosphatasia must not be forgotten as an aetiological factor of abnormally low weight and/or height for age in children and alkaline phosphatase activity should be checked accurately.
Disclosure
The authors declared no competing interests.
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P190

Bone quality and quantity in Duchenne Muscular Dystrophy patients
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The aim of the study is to evaluate bone quantity (aBMD) and bone quality as assessed by TBS in DMD subjects.
43 boys and girls suffering from DMD with a mean age 10.5$\pm$3.7 years and height and weight z-score (Zc) medians of -0.67 and 0.25 s.d. were included in the study. Spine DXA scans were obtained using a GE Lunar iDXA with software v13.31. Lumbar spine trabecular bone texture (TBS) was determined using Med-Imaps custom software to calculate raw values that were subsequently adjusted for tissue thickness based on a normative population of healthy Spanish boys ($n=1468$) and girls ($n=2659$). Subjects were stratified based on tertile approach for TBS and aBMD.
Overall, the mean aBMD Zc of the population was moderate (-1.19 ± 1.19 s.d.) while TBS Zc was normal for age (-0.08 ± 1.32 s.d.). Negative associations were observed between aBMD, Height and weight Zcs and age ($r=-0.56$, -0.43 and -0.51, $P<0.001$) whereas no association was obtained with TBS Zc ($r<0.1$, $P=0.9$). aBMD explained 25% (r^2) of TBS values. Considering subjects in the lowest tertile (LT), 14 subjects were in this tertile based on aBMD or TBS. No differences in terms of age, height and weight Zcs, lumbar tissue thickness or fat percent (all $P>0.7$) were observed between these two group of subjects. The LT cut-off values were 0.582 g/cm^2 for aBMD (Zc$=-0.84$ s.d.) and 1.188 for TBS. Subjects in the aBMD LT have a TBS value normal for age (Zc$=-0.04$ s.d.) while subjects in the TBS LT have a low aBMD for age (Zc$=-0.95$ s.d.). Interestingly, considering the minimum of TBS or aBMD LT values, 21 subjects were classified as low bone status.
As expected, low aBMD was observed in DMD subjects. Interestingly, a normal TBS for age was observed in those patients. aBMD and TBS identified similar number of subjects with low bone status. One striking finding concerns the cut-off value of TBS LT which is similar to that obtain for adults and link to a high risk for fracture (1.188 vs 1.200). In addition, it seems that the combination of aBMD and TBS allows to identify more subjects with low bone status. Further researches are needed to evaluate parameters associated with a low TBS value as well as TBS changes during growth in DMD subjects.
Disclosure
Renaud Winzenrieth is senior scientist at Med-Imaps.
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P191

Evolution of bone quality and quantity in patients suffering from Duchenne Muscular Dystrophy

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The aim of the study is to evaluate, across time, if a bone microarchitectural texture modification exists or not and to evaluate its associations with other bone and body composition parameters.
16 Spanish children suffering from DMD with a mean age 9.7±3.0 years and height and weight z-score of −0.76 and 0.16 SD were included in the study. Spine DXA scans and body composition scans were obtained using a GE Lunar Prodigy at baseline, 12 and 24 months of follow-up. Lumbar spine TBS was determined using Med-Imaps custom software to calculate raw values that were subsequently adjusted for tissue thickness based on a normative population of healthy Spanish boys and girls (n=4127). z-score TBS were evaluated using the same normative population. Variations of mean BMD and TBS during the follow-up were express in SD. z-scores variations of BMD, TBS, height and weight were also assessed
At baseline, BMD and TBS z-scores were −1.1SD and −0.2 S.D. respectively. Both TBS and BMD increased significantly during the follow-up with more marked increase for TBS as express in S.D.. A weak correlation between TBS and BMD variations has been observed (r=0.51). BMD and TBS z-score decreased along the follow-up as well as height and weight. This z-score decreases seems to be more marked on TBS (Δz-score = −0.78 S.D.), Height (Δz-score = −1.04 S.D.) and Weight (Δz-score = −1.39 S.D.) than on Spine BMD (Δz-score = −0.34 S.D.) after 24 months of follow-up. At baseline and 12 months, TBS was associated positively with total fat mass (r^2=0.46, P=0.01 and r^2=0.64, P<0.001) while lean mass, BMD at spine, age, BMI, height were excluded from the model. No association was calculated at 24 months due to a small number of patients.
As expected, both BMD and TBS increase during growth with a weak correlation between BMD and TBS changes (r^2=26%). Although these physiological increases, these values remained below normal values for age. Interestingly, TBS seemed to be associated with the total fat mass while BMD was not. These results suggests that a bone texture impairment exists in DMD and that this impairment varies with growth. Further studies are needed to confirm these preliminary results.

Disclosure

Renaud Winzenrieth is senior scientist at Med-Imaps.

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P192

Low bone mineral density and fractures are prevalent in children with spinal muscular atrophy

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Objectives

Spinal muscular atrophy (SMA) results in varying degrees of hypotonic immobility. Prior reports demonstrate an increased risk of fracture and a trend toward low bone mineral density (BMD) in this population. We aim to further characterize bone health in paediatric SMA patients by reporting the prevalence of fractures and low BMD (z-score ≤ −2.0) by SMA subtype, BMD of the lateral distal femur (LDF; an important fracture location in non-ambulatory children and young adults), and prevalence of osteoporosis according to 2013 ISCD criteria.

Methods

A retrospective chart review was conducted of 86 patients, ages 12 months to 25 years, with confirmed diagnosis of SMA seen from 2005 to 2015. Lumbar spine (LS), total body (TB) and LDF DXA scans were obtained for clinical care; initial DXA scans results are reported herein. Fracture history was recorded at annual clinic visits. Cumulative fracture frequencies from patients' last encounters are reported.

Results

Median age at initial SMA visit was 1.8 years, but differed by SMA subtype. DXA data were available on 69% of patients: of these, 90% had a BMD z-score ≤ −2.0 at first DXA. BMD of all sites was lower with worsening SMA severity. Fractures occurred in 36% of patients, the femur being the most common location (25 of 53 fractures). 13% of patients had multiple fractures.

Conclusion

Low BMD is highly prevalent in SMA patients at time of first DXA. Fracture frequency is also high with predominance of femur fractures in all subtypes. However, few patients met ISCD diagnostic criteria for osteoporosis. Our data suggest poor bone health is a significant concern for SMA patients, but may be underestimated using the 2013 ISCD criteria for diagnosis of osteoporosis in children.

Table 1

	SMA 1 (most severe)	SMA 2 (moderate)	SMA 3 (mild)	*P*-value
Number (*n*)	24	44	18	
Female (%)	15 (63%)	23 (52%)	8 (44%)	0.50
Age (y) at initial neuromuscular visit	0.6 (0.3, 1.1) (*n*=24)	2.0 (0.9, 4.4) (*n*=44)	3.9 (2.1, 8.7) (*n*=18)	0.0003
Age (y) at last encounter	7.6 (2.2, 12.4) (*n*=24)	6.2 (3.5, 12.2) (*n*=44)	12.9 (7.7, 17.9) (*n*=18)	0.01
Age (y) at 1st reported fracture	3.0 (1.9, 6.0) (*n*=11)	6.6 (3.3, 11.1) (*n*=12)	10.4 (9.2, 11.5) (*n*=8)	0.004
Patients ≥1 fracture	11 (46%)	12 (27%)	8 (44%)	0.22
Fractures at femur	13/22 (59%)	7/19 (37%)	5/12 (42%)	0.33
Age (y) at 1st DXA	3.9 (2.8, 4.8) (*n*=14)	5.4 (4.1, 6.6) (*n*=28)	8.1 (5.1, 11.3) (*n*=17)	0.007
LS BMD *z*-score	−4.7 (−5.7, −3.6) (*n*=14)	−2.5 (−3.3, −0.7) (*n*=22)	−0.2 (−1.8, 0.2) (*n*=13)	<0.0001
TB BMD *z*-score	−2.8 (−2.9, −2.2) (*n*=7)	−1.8 (−2.7, −0.5) (*n*=16)	−1.9 (−2.8, −1.6) (*n*=10)	0.25
LDF BMD *z*-scores	(*n*=6)	(*n*=22)	(*n*=13)	0.01
Region 1	−4.5 (−5.1, −3.6)	−3.5 (−4.3, −2.9)	−2.7 (−3.7, −1.1)	
Region 2	−4.6 (−5.8, −3.6)	−3.8 (−4.2, −3.1)	−2.3 (−4.1, −1.4)	0.02
Region 3	−3.9 (−5.1, −3.1)	−2.9 (−3.5, −2.1)	−1.6 (−3.5, −1.3)	0.06
Prevalence of BMD *z*-score ≤ −2.0 at 1st DXA (any site)	14/14 (100%)	25/28 (89%)	14/17 (82%)	0.34
Osteoporosis by ISCD criteria at last encounter	2/14 (14%)	1/28 (4%)	2/17 (12%)	0.07

Data expressed as *n* (%) and median (25th, 75th percentile).

Results

Median age at initial SMA visit was 1.8 years, but differed by SMA subtype. DXA data were available on 69% of patients: of these, 90% had a BMD z-score ≤ −2.0 at first DXA. BMD of all sites was lower with worsening SMA severity. Fractures occurred in 36% of patients, the femur being the most common location (25 of 53 fractures). 13% of patients had multiple fractures.

Conclusion

Low BMD is highly prevalent in SMA patients at time of first DXA. Fracture frequency is also high with predominance of femur fractures in all subtypes. However, few patients met ISCD diagnostic criteria for osteoporosis. Our data suggest poor bone health is a significant concern for SMA patients, but may be underestimated using the 2013 ISCD criteria for diagnosis of osteoporosis in children.

Disclosure

The authors declared no competing interests.

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P193

Aggravated bone density decline following symptomatic osteonecrosis in children with acute lymphoblastic leukemia

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Objectives

Osteonecrosis (ON) and decline of bone mineral density (BMD) are serious side effects during and after treatment of childhood acute lymphoblastic leukemia (ALL). It is unknown whether ON and low BMD co-occur in the same patients, and whether these two osteogenic side-effects can mutually influence each other's development.

Methods

BMD and the incidence of symptomatic ON were prospectively assessed in a national cohort of 466 patients with ALL (4–18 years of age) who were treated according to the dexamethasone-based Dutch Child Oncology Group-ALL9 protocol. BMD of the lumbar spine (BMD_{LS})(n=466) and of the total body (BMD_{TB})(n=106) were measured by dual x-ray absorptiometry. BMD was expressed as age- and gender-matched standard deviation scores (SDS; z-score). Multivariate linear mixed models were adjusted for age at diagnosis.

Results

Thirty patients (6.4%) suffered from symptomatic ON. At baseline, BMD_{LS} and BMD_{TB} did not differ between patients who developed or who did not develop ON. At cessation of treatment, patients with ON had a lower mean BMD_{LS} and BMD_{TB} than patients without ON (respectively, ON+: −2.16 vs ON−: −1.21, P<0.01 and ON+: −1.73 vs ON−: −0.57, P<0.01). Multivariate analyses showed that patients with ON had a steeper BMD_{LS} and BMD_{TB} decline during follow-up than patients without ON (interaction group time, P=0.09 and P=0.04).

Conclusion

We conclude that symptomatic ON and low BMD during antileukemic treatment co-occur in pediatric ALL patients. BMD status at ALL diagnosis does not seem to precede ON. However, the development of ON seems to aggravate BMD decline during antileukemic treatment, most likely due to bone destruction and the advised physical immobilization.

Disclosure

The authors declared no competing interests.

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P194

Results of conservative treatment in patients with phosphate diabetes

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Objective
Bone metabolism was studied in patients with phosphate diabetes before and after medication.
Methods
39 patients with phosphate diabetes age 2–18 years (7.8 ± 4 years, 64% male) and multiplanar deformities of the lower extremities were treated with monthly vitamin D (2000 IU/day), alfacalcidol (0.25 mg/every other day) and calcium glycerophosphate (600 mg/day) for 6 months.
Biochemical indices were evaluated before ($n=39$) and after treatment ($n=5$), Table 1.

Table 1

Indicators of bone metabolism/stages of treatment	Before treatment	After treatment
Ionized calcium	1.21 ± 0.01	1.25† ± 0.02
Serum phosphate	0.62 ± 0.03	0.67 ± 0.07
Calcium	2.34 ± 0.02	2.44† ± 0.03
$25(OH)_2D$	19.30 ± 2.01	40.97* ± 7.07
$1,25(OH)_2D$	74.15 ± 3.89	134.60* ± 13.39
PTH	48.66 ± 4.59	39.01 ± 12.86
Osteocalcin	123.35 ± 10.27	59.11* ± 34.05
Urinary calcium (daily)	2.42 ± 0.25	2.54 ± 0.94
Urinary phosphate (daily)	34.09 ± 1.36	26.52† ± 3.15
P1NP	815.03 ± 59.86	576.4 ± 205.65
B-CTx	2.16 ± 0.11	1.69 ± 0.46

*Significant difference treatment $P<0.05$. †Trend close to significant, $0.1>P>0.05$.

Results
After treatment, 25-hydroxy vitamin D increased 2.12 times ($P<0.05$), 1,25-dihydroxy vitamin D increased 1.8 times ($P<0.05$), and osteocalcin decreased in two times ($P<0.05$).
Strong correlations were observed only between 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D (Table 2).

Table 2

	Ca+	P	Ca	25(OH) 2D	1,25 (OH)2D	PTH	Osteo-calcin	Urine calcium (daily)	Urine phos-phor (daily)	P1NP	B-CTx
Ca+	1.00	0.16	0.24	0.04	0.03	0.06	0.06	0.27	−0.02	0.35	0.02
P	0.16	1.00	0.25	0.27	0.24	0.07	0.19	−0.04	−0.63	0.04	0.04
Ca	0.24	0.25	1.00	0.23	0.52	−0.38	−0.13	−0.18	−0.42	0.24	−0.09
25(OH)2D	0.04	0.27	0.23	1.00	0.80	−0.34	−0.01	−0.30	−0.13	0.06	0.23
1,25(OH) 2D	0.03	0.24	0.52	0.80	1.00	−0.39	−0.38	−0.31	−0.34	−0.04	0.05
PTH	0.06	0.07	−0.38	−0.34	−0.39	1.00	−0.32	0.49	0.37	−0.36	−0.62
osteocalcin	0.06	0.19	−0.13	−0.01	−0.38	−0.32	1.00	−0.02	−0.19	0.52	0.60
urine calcium (daily)	0.27	−0.04	−0.18	−0.30	−0.31	0.49	−0.02	1.00	0.41	0.27	−0.01
urine phos-phor (daily)	−0.02	−0.63	−0.42	−0.13	−0.34	0.37	−0.19	0.41	1.00	−0.13	−0.18
P1NP	0.35	0.04	0.24	0.06	−0.04	−0.36	0.52	0.27	−0.13	1.00	0.74
B-CTx	0.02	0.04	−0.09	0.23	0.05	−0.62	0.60	−0.01	−0.18	0.74	1.00

Correlations (marc vdrr.sta). Marked correlations are significant at $P<0.05000$. $n=39$ (Casewise deletion of missing data).

After treatment, positive correlations were seen between Ca and Ca+, Ca+ and 1,25-dihydroxy vitamin D, 25-hydroxy vitamin D and osteocalcin, 25-hydroxy vitamin D and B-CTx, 1,25 dihydroxy vitamin D and P1NP, urinary calcium and urinary phosphate, B-CTx and osteocalcin. Negative correlations were observed between PTH and 1,25-dihydroxy vitamin D, PTH and B-CTx, urinary phosphate and osteocalcin, B-CTx and urinary phosphate. (Table 3)

Table 3

	Ca+	P	Ca	25(O-H)2D	1,25(-OH)2D	PTH	Osteo-calcin	Urine calci-um (daily)	Urine phos-phor (daily)	P1NP	B-CTx
Ca+	1.00	0.11	0.85	−0.35	0.86	−0.50	0.28	0.61	0.06	0.48	0.03
P	0.11	1.00	−0.37	−0.60	−0.12	0.69	0.28	0.70	0.59	0.18	−0.53
Ca	0.85	−0.37	1.00	−0.16	0.75	−0.70	−0.23	0.18	−0.25	0.24	0.16
25(OH)2D	−0.35	−0.60	−0.16	1.00	0.16	−0.57	0.90	−0.66	−0.68	0.40	0.92
1,25(OH) 2D	0.86	−0.12	0.75	0.16	1.00	−0.79	0.18	0.38	−0.21	0.75	0.52
PTH	−0.50	0.69	−0.70	−0.57	−0.79	1.00	−0.41	0.20	0.56	−0.50	−0.78
Osteocalcin	−0.28	−0.28	−0.23	0.90	0.18	−0.41	1.00	−0.56	−0.75	0.64	0.89
Urine calcium (daily)	0.61	0.70	0.18	−0.66	0.38	0.20	−0.56	1.00	0.77	0.18	−0.46
Urine phos-phor (daily)	0.06	0.59	−0.25	−0.68	−0.21	0.56	−0.75	0.77	1.00	−0.41	−0.75
P1NP	0.48	0.18	0.24	0.40	0.75	−0.50	0.64	0.18	−0.41	1.00	0.68
B-CTx	0.03	−0.53	0.16	0.92	0.52	−0.78	0.89	−0.46	−0.75	0.68	1.00

Correlations (marc vdrr.sta). Marked correlations are significant at $P<0.05000$. $n=5$ (Casewise deletion of missing data).

Conclusions
The medication protocol improves bone metabolism with phosphate diabetes, reduces osteomalacia, and improves ratios of bone formation and bone resorption.
Disclosure
The authors declared no competing interests.
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P195

Increase of bone mineral density in patients with osteogenesis imperfecta treated with pamidronate disodium.

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Objective
This study aimed to evaluate the efficacy of the treatment with pamidronate disodium (PD) with respect to the increase of bone mineral density (BMD) in patients with osteogenesis imperfecta (OI).
Patients and methods
We evaluated nine patients (six boys) with OI (four with type III, four with type IV, one with type I) treated with PD from 4.68 to 7.92 years (mean ± S.D.: 6.75 ± 1.38 years). Intravenous PD was administered in a 1 mg/kg single daily dose for three sequential days at 4-month intervals. For each patient BMD was evaluated twice through dual-energy x-ray absorptiometry (DEXA-scan): the first DEXA-scan was performed before or up to 0.72 years after the beginning of the treatment (mean age: 6.69 ± 1.11 years), and the second DEXA-scan was performed 0.94 to 2.8 years after the first one (interval between the two DEXA-scans: 1.86 ± 0.64 years). The values of lumbar spine (L1–L4) BMD z-score in the first DEXA-scan (Z1) and in the second DEXA-scan (Z2) were compared through paired Student's t-test (P-values <0.05 were significant).
Results
The values of Z1 and Z2 ranged respectively between −2.8 and −7.9 (mean ± S.D.: −5.12 ± 1.59) and between −1.76 and −5.1 (mean ± SD: −3.44 ± 1.21). The mean of Z2 was significantly higher than the mean of Z1 ($P=0.0002$). In all patients the values of Z2 were higher than the values of Z1 and the difference Z2–Z1 varied between 1.12 and 3.52 (mean ± SD: 1.80 ± 0.76). The increase of lumbar BMD z-score varied between 14 and 53% (mean ± SD: 33 ± 12).
Conclusion
The significant improvement of BMD in patients with OI treated with PD shows that this treatment increased bone mineral accretion efficiently.
Disclosure
The authors declared no competing interests.
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P196

Early onset cataract in an infant with activating calcium sensing receptor mutation

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Background
A 3 month-old boy was born at term, to non-consanguineous parents by spontaneous vaginal delivery, in good condition, weighing 4.19 kg. Newborn examination, including eyes, was normal prior to discharge. He has two older brothers in good health.
Presenting problem
He was admitted at 7 days of life with focal seizures and hypocalcaemia (1.5 mmol/l), hypomagnesaemia (0.6 mmol/l), hyperphosphataemia (3.7 mmol/l) and inappropriately low parathyroid hormone levels (<0.3 pmol/l). He was treated with intravenous calcium and magnesium infusions and discharged home on oral calcium, magnesium and alfacalcidol. He was re-admitted at five weeks with recurrent focal seizures and hypocalcaemia that persisted despite intravenous calcium infusions. Parents noticed he had stopped fixing and following over the previous week. Eye examination revealed nystagmus and absent red reflexes. He was urgently reviewed by Ophthalmology who confirmed presence of dense bilateral cataract.
Clinical management
An activating variant in the calcium sensing receptor (CaSR) gene was suspected and confirmed by genetic analysis. He was commenced on a subcutaneous parathyroid hormone infusion and weaned off intravenous calcium infusion. Alfacalcidol was stopped and colecalciferol was started. Thiazide diuretics were commenced to reduce renal calcium excretion. CSF analysis and MRI brain were normal. Ultrasound abdomen showed mild nephrocalcinosis. Urine calcium creatinine ratio was regularly monitored. Seizures settled after resolution of hypocalcaemia. He was operated for cataract at nine weeks of life.
Discussion
The CaSR is a Class C G-protein coupled receptor which senses extracellular levels of calcium ion. Activating CASR gene variants result in an increased calcium sensitivity in parathyroid and renal cells, which in turn reduces the parathyroid set point and reduces renal calcium reabsorption despite prevailing hypocalcaemia. The clinical presentation varies from mild paraesthesia and muscle cramps to nephrocalcinosis, nephrolithiasis, basal ganglia calcifications and seizures, while some remain asymptomatic.
Cataracts are a recognised complication of hypoparathyroidism. However, as far as we are aware, this is the first reported case of cataract in an infant with activating CASR mutation, although it has been previously identified in mouse models. We therefore suggest that evaluation for cataract is required in this subgroup of patients.
Disclosure
The authors declared no competing interests.

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P197

Benign osteopetrosis associated with homozygous mutation in CLCN7

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Introduction
Benign osteopetrosis type 2 (OPTA2) (Albers-Schönberg disease) is usually associated with a heterozygous mutation in *CLCN7*. Patients may be asymptomatic and present following an x-ray taken for other reasons or with a low trauma fracture. There may be a family history. Homozygous mutations in *CLCN7* usually result in severe disease which presents in the neonatal period or early infancy. We present a case of benign osteopetrosis associated with a homozygous variant in *CLCN7* that was diagnosed incidentally.
Presenting problem
A 6 year-old girl was referred to the metabolic bone clinic for an opinion on increased bone density. She had been noted to have a heart murmur for which she had had a chest x-ray. This had shown generalised increase in bone density. Further investigation of the heart murmur showed this to be caused by a small ASD which was asymptomatic. She had no history of fractures and was otherwise quite well. Both parents are well as are her two sisters. The parents are consanguineous.
Clinical management
Further investigations revealed a very high bone density (BMD z-score $+6.1$) but routine biochemistry was all normal. Genetic analysis of genes for osteopetrosis showed a homozygous variant in *CLCN7*. *LRP5* mutation analysis was negative. DXA scans of her two sisters showed that her older sister has a normal BMD but her younger sister's BMD is $+2.3$. Father's BMD was also normal. Mother has not had a DXA as she is pregnant. Genetic analysis of the other family members is awaited. Because of the lack of symptoms, she has not had any specific treatment.
Discussion
Homozygous mutations in *CLCN7* usually give rise to osteopetrosis with severe disease whilst heterozygous mutations cause mild, often asymptomatic disease. This case is unusual in that she has a genotype suggestive of severe disease with a mild phenotype. It is currently not clear if the variant is contributing to her clinical phenotype and further family studies are ongoing to try to establish this.
Disclosure
The authors declared no competing interests.

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P198

Impaired mobility and pain significantly impact the quality of life of children with X-linked hypophosphatemia

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X-linked Hypophosphatemia (XLH), the most common heritable form of rickets, is a disorder of renal phosphate wasting caused by high circulating levels of fibroblast growth factor 23 (FGF23) that impairs normal phosphate reabsorption in the kidney and production of the active form of vitamin D. Affected children present with hypophosphatemia resulting in rickets, bowing of the legs and short stature. Limited information is available about the disease burden in children with XLH.
Objectives
The objective was to characterize the clinical condition of children with XLH and assess the impact on function and quality of life.
Methods
An IRB-approved, web-based questionnaire was completed by parents on behalf of children with XLH. Pain and disability were assessed by parent report using the POSNA PODCI (Pediatric Orthopedic Society of North America Patient Outcomes Data Collection Instrument) and SF-10 Health Survey for Children. English and French versions were available.
Results
71 pediatric surveys were completed for children from 1–17 years of age with a median age of 8 years (9 in the 0–4, 48 in the 5–12, 14 in the 12–18 age groups respectively). Reported skeletal abnormalities included bowing of the tibia/fibula (52/71 (73%)), bowing of the femur (45/71 (63%)), gait disturbance (61/71 (86%)), joint pain (46/71 (65%)), bone pain (42/71 (59%)), joint stiffness (30/71 (42%)) and short stature (57/71(80%)). Over 30% of responders had undergone at least one surgery to correct a skeletal defect. Mean POSNA PODCI domain scores for XLH children with bone or joint pain were as follows: transfer and basic mobility 40.8 (18.6), Sports and physical functioning 29.4 (19.6), pain/comfort 34.3 (16.1), happiness 35.0 (17.5) and global functioning 35.0 (17.2). The mean SF-10 physical health summary (PHS) score for children with bone or joint pain was 33.5 (16.4). Scores were similar in the 5–12 and 12–18 age groups. For all PODCI and SF-10 scales, the mean score in a general population of healthy children is 50 (S.D. $=10$) with higher scores indicating better health.
Conclusion
Children with XLH experience significant skeletal deformity with associated bone pain, joint pain, and joint stiffness that restrict range of motion, impair gait and diminish physical health status relative to peers. Limitations of this study include the small sample size, particularly in early childhood and adolescence, and the responder selection bias associated with the use of an online survey.
Disclosure
Authors associated with Ultragenyx Pharmaceutical Inc. are employees of Ultragenyx Pharmaceutical Inc. which is the company that sponsored the study

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LRP5-associated high bone mass disorder: novel familial mutation in LRP5 and investigation of bone mineralization density distribution (BMDD)

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Mutations in LRP5 cause a variety of phenotypes, including high bone mass and low bone mass disorders. In patients with high bone mass, different heterozygous mutations have been described, all of them clustering in a region including the binding pocket for DKK1 and sclerostin. The pathogenic mechanism is thought to be a gain-of-function mediated by an impaired inhibition of the canonical Wnt signalling pathway, thereby leading to increased bone modelling.
We report on two affected family members, a mother and her daughter, exhibiting high bone mass (T-scores L-spine 11.4 SD., femur 10.5 SD.), increased calvarial thickness (Figure 1), and thickened cortices of the long bones, without fracturing. The mother did not report any symptoms while the daughter had congenital hearing impairment with subsequent cochlear implantation, recurrent facial palsy, and migraine. In addition, there was stenosis of the foramen magnum present in the daughter.
In both individuals, we detected a novel heterozygous in-frame insertion of two amino acids in the LRP5 gene, very likely associated with a gain-of-function. In the daughter, part of the occipital squama was surgically removed and the bone sample was used for Bone Mineralization Density Distribution (BMDD) determination by quantitative Backscattered Electron Imaging (qBEI) (Figure 1). The bone sample consisted of two different regions: one region without bone remodelling, lower and less heterogeneous bone matrix mineralization, and another region with osteonal remodelling, increased and a more heterogeneous mineralization. The higher mineralization is reflecting a higher average tissue age.

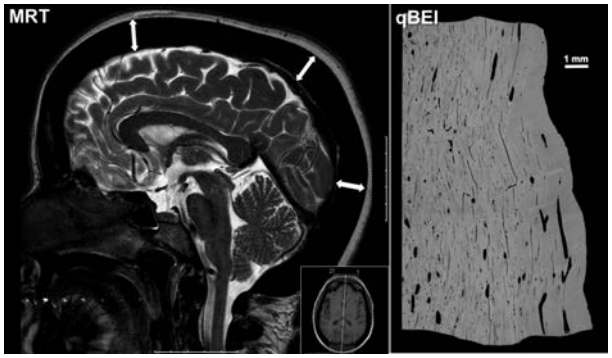

Figure 1 Cranial MRT (left) and qBEI of occipital squama (right).

In summary, we present a novel LRP5 mutation associated with high bone mass in two related individuals. Furthermore, we show qBEI data of an occipital bone sample, exhibiting two different regions of bone remodelling and mineralization.
Disclosure
The authors declared no competing interests.
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P200

Relationship of lipid parameters and insulin resistance with bone health in South Korean adolescents

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Objectives
To prevent future osteoporosis, it is important to identify factors that affect bone health in adolescents as well as adults. This study aimed to examine the relationship between lipid profiles and insulin resistance and BMC in Korean adolescent population.
Methods
Data from 706 boys and 621 girls who participated in the Korea National Health and Nutrition Examination Survey from 2008 to 2011 were analyzed. Lipid profiles were measured, and homeostasis model assessment of insulin resistance (HOMA-IR) was calculated to assess insulin resistance. BMC was measured at the total femur, femur neck, and lumbar spine by using whole-body dual-energy x-ray absorptiometry.
Results
Triglyceride level and HOMA-IR were negatively correlated with BMC at all 3 sites in boys. In girls, triglyceride level showed a negative correlation with BMC at the femur neck and lumbar spine, and HOMA-IR was negatively associated with BMC only at the femur neck. The adjusted odds ratios (ORs) for the highest BMC tertile group at the total femur and lumbar spine were significantly decreased as triglyceride level increased and the ORs for the highest BMC tertile group at lumbar spine was decreased according to increasing total cholesterol level in boys. In girls, the ORs for the highest BMC tertile group at all 3 sites were also decreased as triglyceride level increased. The value of BMC at femur neck and total femur was negatively associated with HOMA-IR only in boys.

Table 3 Adjusted ORs (CIs) for highest tertile group of BMC according to lipid parameters and insulin resistance.

	Boys			Girls		
	Femur neck	Total femur	Lumbar spine	Femur neck	Total femur	Lumbar spine
TC	0.97 (0.93, 1.01)	0.99 (0.95, 1.04)	0.94 (0.88, 0.997)	0.92 (0.87, 0.97)	0.95 (0.90, 1.01)	0.97 (0.93, 1.02)
LDL-C	0.98 (0.93, 1.03)	1.01 (0.96, 1.06)	0.95 (0.89, 1.02)	0.94 (0.89, 1.00)	0.95 (0.89, 1.02)	0.99 (0.93, 1.05)
HDL-C	1.05 (0.92, 1.19)	1.11 (0.98, 1.24)	1.01 (0.89, 1.15)	0.96 (0.83, 1.11)	1.03 (0.90, 1.18)	0.96 (0.86, 1.08)
TG[a]	0.74 (0.47, 1.18)	0.56 (0.35, 0.897)	0.52 (0.34, 0.8)	0.33 (0.17, 0.65)	0.55 (0.32, 0.96)	0.57 (0.35, 0.92)
HOMA-IR[a]	0.49 (0.27, 0.88)	0.42 (0.21,0.83)	0.74 (0.39, 1.38)	0.64 (0.27, 1.52)	0.77 (0.39, 1.51)	0.61 (0.28. 1.32)

BMC, bone mineral content; HOMA-IR, homeostasis model assessment of insulin resistance; OR, odd ratio; TC, total cholesterol; TG, triglyceride. Values were obtained by using a multi van able logistic regression analysis after adjustment for age, weight, height, daily energy and calcium intake, alcohol intake, smoking status, physical activity, serum 25-hydroxyvitamin D3, and menarche (in girls).
[a]Log transformation was performedfor analyses.

Conclusion
BMC was inversely associated with triglyceride and HOMA-IR in boys and triglyceride in girls.
Disclosure
The authors declared no competing interests.
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P201

The results of pamidronate treatment independently and in combination with surgery in patients with osteogenesis imperfecta.

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Introduction
The effectiveness of intravenous pamidronate was assessed independently and in combination with corrective osteotomy surgery for lower extremity deformities in children with osteogenesis imperfecta.

Methods

Orthopaedic treatment was conducted in 21 patients with OI (type I–ten patients, type III–11 patients), including 13 males and eight females with mean age 9.4 ± 0.6. All patients received calcium supplements and active forms of vitamin D. Pamidronate was administered cyclically during the year and controled by serum calcium level. Cycles were separated by three month intervals. In type I of OI, withC-Terminal Telopeptide or CTX of 0.5–1.5 ng/ml, *z*-score −2.5 to −3.5, pamidronate was administered at 0.5 mg/kg per cycle. In type III OI (CTX 1.5–3.5 ng/ml, *z*-score −3.5 and below), pamidronate was administered at 1 mg/kg per cycle. Pamidronate was administered independently in ten patients an in conjunction with surgery in 11 patients.

Results

Treatment outcomes were evaluated clinically (number of fractures, gait recovery) and biochemically (CTX as bone resorption marker) after 6 months in all patients and by lumbar spine DEXA *z*-score after a year of treatment in 18 patients. After treatment, 18 patients had no repeat pathological fractures, two patients sustained femur fractures and one sustained a tibia fracture. Among operative patients, only four were independent ambulators before surgery; by 1.5 years after surgery, nine of 11 patients were ambulatory. Among all patients, the mean CTX decreased by 0.46 (37%), $P = 0.021$ and mean *z*-score increased by 1.13 (27%). Patients who underwent surgery experienced less decrease in CTX (0.26 ng/ml) than those who did not (0.67) due to the increased bone turnover associated with osteotomy healing.

Conclusions

The use of pamidronate independently or in combination with corrective osteotomies in patient with osteogenesis imperfecta leads to fewer pathologic fractures, decreased bone turnover, and increased bone density, and in combination with corrective osteotomies may facilitate improved ambulatory status.

Disclosure

The authors declared no competing interests.

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