Bone Abstracts

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9th International Conference on Children's Bone Health

22–25 June 2019, Salzburg, Austria

ICCBH
9TH INTERNATIONAL CONFERENCE ON CHILDREN'S BONE HEALTH
22-25 June 2019
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Abstract book

Welcome

Dear Colleagues

We are delighted to organise the 9th International Conference on Children's Bone Health, to be held 22–25 June 2019 in the beautiful Austrian city of Salzburg.

This Conference brings together scientists and clinicians from a wide range of disciplines to gain a better understanding of the growing skeleton in health and disease. The scope ranges from basic molecular mechanisms to clinical aspects, from bone physiopathology to treatment. We invite anyone with an interest in bone metabolism and bone mass in children, adolescents and young adults to attend. The ICCBH conference takes place every two years and is attended by over 500 delegates from across the globe, making it truly multinational and multidisciplinary –a unique networking opportunity.

The scientific programme is designed to present researchers, physicians, and allied health professionals with the newest research, with sessions including plenary lectures by world-leading experts, symposia, workshops, oral communications and poster sessions.

The Conference offers investigators from around the world an opportunity to meet with each other and with industry representatives. There will be plenty of opportunity for discussion both in and outside the lecture theatre.

We are proud to hold this conference in one of the most beautiful cities of Europe. Famous as the birthplace of Mozart, Salzburg is well known for its romantic scenery and rich cultural heritage. The conference venue is the Salzburg Congress Center, a versatile, modern and spacious venue, perfect in size and location for ICCBH.

ICCBH is your opportunity to hear about and discuss the newest developments in our understanding of paediatric bone health. We welcome your participation in a lively interactive meeting with the leaders in the field!

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Awards

New Investigator Awards

The following awards were made by the Scientific Programme Committee based on scores achieved during the abstract review process.

Fawaz Arshad (Sheffield, United Kingdom), OC18
Iris Boraschi-Diaz (Montreal, Canada), OC12
Stephanie Borg (Sheffield, United Kingdom), OC4
Alessandra Cocca (London, United Kingdom), P221
Elizabeth Curtis (Southampton, United Kingdom), OC5
Ahmed Elhakeem (Bristol, United Kingdom), OC1
David Fennimore (Sheffield, United Kingdom), P93
Gali Guterman Ram (Bethesda, United States), OC21
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Joseph Kindler (Philadelphia, United States), P94
Lucinda Lee (Westmead, Australia), OC11
Laura Leoni (Pavia, Italy), P37
Rebecca Moon (Southampton, United Kingdom), P154
Sonal Palande (Pune, India), OC2
Kristen Pan (Bethesda, United States), P220
Marie-Eve Robinson (Montreal, Canada), P150
Sumudu Nimali Seneviratne (Colombo, Sri Lanka), P16
Shinji Takeyari (Osaka, Japan), OC13
Francesca Tonelli (Pavia, Italy), OC19
Volha Zhukouskaya (Le Kremlin Bicôtre, France), P51

On site awards

Best Poster

Jeremy Allgrove (London, UK), P117
Klara Maratova (Prague, Czech Republic), LB7

Best Oral Communication

Iris Boraschi-Diaz (Montreal, Canada), OC12
Leanne Ward (Ottawa, Canada), OC14

Slemenda Award

The 2019 Charles Slemenda Award was awarded to Nick Bishop (Sheffield, UK) in recognition of his outstanding contribution to children's bone research.

Previous winners

2017 Frank Rauch (Montreal, Canada)
2015 Zulf Mughal (Manchester, UK)
2013 Maria Luisa Bianchi (Milan, Italy)
2009 Michael Whyte (St Louis, USA)
2007 Ailsa Goulding (Dunedin, New Zealand)
2005 Jean-Philippe Bonjour (Switzerland, Geneva)
2002 John Pettifor (Johannesburg, South Africa)
1999 Francis Glorieux (Montreal, Canada)

CONTENTS

Invited Speaker Abstracts

IS1

Highlights in basic bone research

Matthew Warman
Boston, USA.

Abstract unavailable.

DOI: 10.1530/boneabs.7.IS1

IS2

Highlights in clinical bone research

Nick Shaw
Department of Endocrinology & Diabetes, Birmingham Children's Hospital and Institute of Metabolism & Systems Research, University of Birmingham, Birmingham, UK.

Over the past two years we have continued to see new developments and findings in paediatric bone disease that will help change and modify our clinical practice. I have selected some pertinent publications and divided these into different themes that I intend to highlight in this presentation. These include:

(1) New treatment options – Burosumab for X-linked Hypophosphataemic Rickets and Anti-Sclerostin antibody for Osteogenesis Imperfecta.
(2) New conditions and management – a novel form of Vitamin D dependant rickets and a consensus statement on Pseudohypoparathyroidism.
(3) Longitudinal follow up studies – femoral fractures in Osteogenesis Imperfecta, scoliosis in Fibrous Dysplasia, vertebral fractures in Leukaemia and following discontinuation of Denosumab.
(4) Vitamin D – new evidence of potential benefits or lack of benefit in infections, fracture risk and bone density.

Disclosure
The author declared no competing interests.

DOI: 10.1530/boneabs.7.IS2

IS3

Biomechanics of fetal movements

Niamh Nowlan
Department of Bioengineering, Imperial College London, London, UK.

Mechanical stimulation generated by fetal kicking and movements is known to be important for prenatal musculoskeletal development. The most common human condition in which there is a link between abnormal fetal movements and delayed or impaired skeletal development is developmental dysplasia of the hip (DDH). DDH is a hip joint shape abnormality, with risk factors being associated with restricted fetal movement, such as fetal breech position and oligohydramnios. Evidence suggests that movements late in gestation are particularly important for normal hip joint development, as even short-term breech positioning at this stage is associated with an increased risk of DDH. We quantify the mechanical stimulation of the human fetal hip joint over gestation, for both normal and abnormal intrauterine environments, in order to investigate the link between a change in the biomechanics of the developing hip joint, and the risk of DDH after birth. We combined advanced fetal imaging with computational modelling techniques to predict the mechanical stimulation in the developing limb over the second half of gestation. Furthermore, we have modelled a range of intra-uterine conditions and situations which increase the risk of DDH, such as fetal breech position and oligohydramnios (reduced amniotic fluid), in order to be able to understand how a range of factors affecting movement may impact on the developing hip joint. We demonstrate that the stresses and strains acting in the hip joint are significantly reduced when a baby is in breech position, or suffers from oligohydramnios. We also reveal a trend of reduced stimulation in the joints of first-born children (who are also at a greater risk of DDH). Developmental biomechanics research can shed new light on the link between fetal movements and growth and morphogenesis, and thus inform future diagnostic and preventative measures for neonatal musculoskeletal conditions.

Disclosure
The author declared no competing interests.

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IS4

Mechanical loading and bone development – insights from epidemiological studies

Jon Tobias
Musculoskeletal Research Unit, Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK.

Mechanical loading exerts a major influence on the size, shape and structure of the skeleton attained in early adulthood, an important determinant of osteoporotic fracture risk in later life. In studies of exercise interventions in children intended to optimise skeletal development, activities associated with relatively high impacts are generally more effective, in line with findings from laboratory studies that bone is exquisitely sensitive to high impacts producing transient skeletal deformation. Epidemiological studies have sought to explore these relationships at different periods, based on a range of methods for evaluating loading and bone development. Recent studies have highlighted the role played by mechanical loading in early life. For example, breech position in the last trimester, which constrains fetal limb movement, is associated with reduced neonatal whole body mass, reduced hip bone mass at age 4, and reduced tibial cortical bone mass at age 17. In addition, we recently found that males born to mothers with oligohydramnios have relatively narrow hips at age 17, ascertained by statistical shape modelling applied to DXA scans. Mechanical loading has also been examined in infancy, as illustrated by findings that age of walking is related to hip strength at age 63, and motor development assessed at age 18 months to hip strength at age 17. Another important focus has been the study of relationships between physical activity, assessed by 7 day accelerometry, and bone development in later childhood. For example, greater participation in vigorous physical activity was associated with greater tibial cortical bone mass at age 15, whereas an equivalent benefit was not seen with moderate activity. Subsequent findings suggest these benefits may be related to the number of bouts of vigorous activity, as opposed to total duration of activity. In further studies, using a device to record impacts within specific g-bands, impacts greater than 4 g (equivalent to running at $>$ 10 km/hour) were found to be associated with greater hip strength and tibial cortical bone mass. Questionnaire based approaches have also been successfully applied, exemplified by positive associations between participation in sporting activity in young adulthood and tibial cortical bone size in men aged 80 years. Taken together, epidemiological studies suggest that mechanical loading plays an important role in bone development, leading to long lasting benefits for skeletal health.

Disclosure
The author declared no competing interests.

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IS5

Spine development

Vincente Gilsanz
Los Angeles, USA.

Abstract unavailable.

DOI: 10.1530/boneabs.7.IS5

IS6

Nutritional rickets – a socioeconomic problem

Wolfgang Högler
Linz, Austria.

Rickets and osteomalacia are caused by calcium deprivation, meaning the body has insufficient calcium supply and the resulting secondary hyperparathyroidism leads to excessive bone resorption and, via renal phosphate wasting, also to hypomineralization of bone and growth plates. The two main environmental causes of calcium deprivation are dietary calcium deficiency and solar vitamin D deficiency. The environmental nature of rickets and osteomalacia is undisputed. On a global scale, hundreds of millions of people are affected, and most are undiagnosed. The fact that rickets is most prevalent in the developing world might suggest that poverty is an important factor, in countries with lacking prevention programs, limited food supply or limited UV sunlight. However, rickets and osteomalacia have become a global health concern as they affect humans of all ages whose diets are low in calcium or whose cultural traditions block sunlight. Dark skinned people are at greatest risk, and their migration to high latitude countries is testing how well rickets prevention programs are implemented. Governmental policies and societal/consensus recommendations have very limited effect unless policy is implemented by systematic monitoring of adherence and by providing financial incentives for those delivering the prevention program and for parents attending the child surveillance visits. Delivering continued education of doctors, health care professionals, and specifically new parents is also paramount. Vaccinations programs and vitamin D supplementation should go hand-in-hand in infants but some countries chose to only monitor vaccinations, which is one of the explanations for substantial regional differences in adherence to rickets prevention programs. Effective prevention includes provision of calcium-rich food, sunlight exposure and/or vitamin D supplements. We have demonstrated that fortification of wheat flour with vitamin D is cost-saving and the optimal strategy to prevent vitamin D deficiency. Supplementing the at-risk groups combined with a flour fortification policy offers a more effective and cost-effective option. Worldwide, billions are spent on 25OH vitamin D testing when the cost of measuring 25OHD in one blood sample is similar to supplementing someone for a whole year. Since the risk groups for rickets and osteomalacia are easily recognizable, supplementation, not testing, should become the new standard.

Disclosure

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IS7

Effect of vitamin D on body composition

Hope A Weiler
Nutrition Research Division, Food Directorate, Health Products and Food Branch, Health Canada; School of Human Nutrition, McGill University.

In Canada, and many other countries, a vitamin D supplement of 400 IU/day is recommended for breastfed infants and staple foods are fortified with vitamin D in accordance with public health policy for the primary prevention of rickets. Both vitamin D receptors and 1-alpha hydroxylase enzymes are expressed in human muscle, implicating vitamin D status and metabolism in growth and development. In a randomized dose response study of vitamin D supplementation (400, 800, 1200, or 1600 IU/day) in infants ($n=132$) from 1 to 12 mo of age, 98% achieved 50 nmol/l 25-hydroxyvitamin D. Infants that achieved vitamin D status above 75 nmol/l of 25-hydroxyvitamin D had elevated percent lean mass and reduced fat mass at 12 mo of age while accounting for sex, length and macronutrient intakes, compared to those below 75 nmol/l. Upon follow-up, fat mass remained lower at 3 y of age. In a subgroup analysis of infants with low vitamin D status below 50 nmol/l at inception ($n=18$), those who received 1200 IU/day of vitamin D demonstrated higher lean mass accretion from 1 to 3 mo of age compared to those receiving a dosage of 400 IU/day. In an ongoing randomized trial of 400 vs 1000 IU/day of vitamin D in infants born with low vitamin D status (<50 nmol/l 25-hydroxyvitamin D; $n=87$), whole body lean mass was higher at 6 mo of age in the group randomized to 1000 IU/day of vitamin D, while accounting for sex, season, skin pigmentation and gestational age at birth. Similarly, in children 2 through 8 y of age ($n=51$) randomized to consume milk products (yogurt beverage and cheese) fortified with vitamin D (300 IU/day) vs. control for 6 mo, percent change in lean mass was enhanced in the intervention group. These controlled studies in infants and young children offer high-level evidence that achievement of population targets for vitamin D intakes and status supports a lean body mass phenotype.

Disclosure

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IS8

Vitamin D in pregnancy and offspring immunology

Catherine Hawrylowicz[1], Eve Hornsby[1], Charlotte Cheadle[1], Paul Pfeffer[1], Nancy Laranjo[2], William Cruikshank[3], Marina Tuzova[3], Augusto A Litonjua[2,4], Scott T Weiss[2,4], Vincent J Carey[2,4] & George O'Connor[3]
[1]Asthma UK Centre for Allergic Mechanisms in Asthma, School of Immunology and Microbial Sciences, College London; [2]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston; [3]Pulmonary Center, Department of Medicine, Boston University School of Medicine, Boston; [4]Harvard Medical School, Boston.

Vitamin D deficiency in pregnancy is common, and is linked to increased risk of adverse outcomes including preterm birth, preeclampsia, infection, gestational diabetes and asthma. Vitamin D possesses well-recognized immunomodulatory functions, and programming of the immune system during foetal development can influence asthma-related risk factors and health outcomes in later life. We hypothesized that influencing vitamin D status during pregnancy would impact the immune profile of the baby at birth. The effect of maternal supplementation with 4400 IU/d vitamin D3 from the end of the first trimester of pregnancy through to term on neonatal immunity was investigated using a subset of cord blood samples from a randomized, double-blind, placebo-controlled clinical trial (the Vitamin D Antenatal Asthma Reduction Trial). Cord blood samples from neonates born to mothers supplemented with 4400 IU/d ($n=26$) or 400 IU/d ($n=25$) of vitamin D3 were analysed for immune cell composition and function by flow cytometry quantitative PCR, and cytokine secretion by cytometric bead array. Higher maternal supplementation of 4400 IU/d resulted in an enhanced broad-spectrum pro-inflammatory cytokine response to TLR-ligation and mitogen stimulation, that corresponded with higher gene expression for select TLR, a trend for increased frequency of myeloid dendritic cells and a four-fold increase in IL-17A secretion following T cell receptor stimulation. Parallel *in vitro* studies increasingly implicate immunoregulatory pathways in the neonate that are distinct from those in adults, and emerging data on a potential role for neutrophils will be discussed. We conclude that increasing vitamin D status in the mother during pregnancy influences the immune profile of her baby. This is predicted to have a beneficial impact and reduce asthma-related risk factors, such as infection, in early life.

Disclosure

The authors declared no competing interests.

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IS9

Osteoclast disorders

Cristina Sobacchi[1,2], Eleonora Palagano[1,2], Ciro Menale[1,2] & Anna Villa[1,3]
[1]CNR-IRGB, Milan Unit, Milan, Italy; [2]Humanitas Clinical and Research Center IRCCS, Rozzano, Italy; [3]San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), San Raffaele Hospital, Milan, Italy.

Osteoclasts are giant multinucleated skeletal cells of hematopoietic origin primarily responsible for bone resorption. Their functional impairment disturbs bone homeostasis and, to a variable extent, a number of other processes, such as growth, hematopoiesis and immune function. The accumulation of bone tissue owing to failure in bone resorption results in increased bone density, which is the hallmark of osteopetrosis (OP), a heterogeneous group of monogenic disorders with autosomal recessive or dominant or X-linked inheritance pattern. Depending on the affected gene, OP arises from a defect of OC resorptive function ('OC-rich' forms) or more rarely from an OC differentiation defect ('OC-poor' forms). The natural course of the disease often comprises severe complications and death during childhood. On the other hand, an increasing number of patients surviving

until adulthood without a cure (hence classified as intermediate) are being reported, which raises questions regarding long-term prognosis and disease mechanisms. Over the last 20 years, the elucidation of the genetic basis of human OP has been crucial for diagnosis, prognosis and treatment and, more in general, has contributed to understand basic bone biology mechanisms. In addition, in recent years Next Generation Sequencing technologies have allowed identifying new genetic defects in single patients with peculiar phenotypes. Most of them affect genes already known to play a role in bone homeostasis (TRAF6, LRRK1, MITF, CSF1R, RELA, ITGB3); nonetheless, in some cases, the underlying pathogenic mechanism still has to be clarified. At present, about 10% of OP patients lack a molecular classification; in these cases, new, unexpected genes could be affected or known genes could harbor elusive defects. In order to fill the gap, we will need to find strategies integrating the technological power of NGS technologies and a better capacity to interpret genomic variations. In my presentation, I will review current knowledge of the molecular and cellular aspects of OP and highlight open questions for future research.

Disclosure

The authors declared no competing interests.

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IS10

Endoplasmic reticulum stress in osteoblasts

Roberta Besio, Francesca Tonelli, Nadia Garibaldi, Laura Leoni, Silvia Cotti & Antonella Forlino
Department of Molecular Medicine, Biochemistry Unit, University of Pavia, Pavia, Italy.

Bone tissue homeostasis requires the coordinated activity of osteoblasts, the bone forming cells, of osteoclasts, the bone resorbing cells, and of osteocytes, generally referred as the bone mechano-sensors. In this contest, osteoblasts are the mesenchymal cells secreting the extracellular matrix components on which hydroxyapatite crystals are then deposited. The most abundant protein of this organic matrix is type I collagen, a heterotrimeric secretory protein, synthesized as procollagen precursor in the endoplasmic reticulum (ER) where it undergoes a series of post translational modification events necessary for proper folding, secretion, extracellular processing and self-assembly in collagen fibers. Mild ER stress in osteoblasts is a physiological event during osteoblasts differentiation, whereas constitutively prolonged and severe ER stress negatively affects osteoblasts homeostasis, causing the activation of unfolded protein response, leading to apoptosis, and ultimately impairing the bone properties. Osteogenesis imperfecta (OI) is a collagen-related heritable disorder affecting several connective tissues, but mainly characterized by skeletal deformity and bone fragility. Together with the dominant forms caused by collagen type I mutations and representing over 85% of OI cases, recessive and X-linked OI have been also described, characterized by defects in proteins involved in collagen type I folding, post-translational modifications, intracellular trafficking, extracellular processing or in proteins important for osteoblasts maturation. Traditionally, the OI bone phenotype was attributed only to the reduced amount or to the presence of structurally abnormal collagen type I in the extracellular matrix. In the last decade it became clear, from our research as well as from data from other groups, that the accumulation of abnormal collagen in the endoplasmic reticulum is responsible for ER stress and indeed is modulating the OI bone outcome. In vitro and in vivo studies using OI models support this conclusion and will be presented and discussed.

Disclosure

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IS11

Clock genes and bone and mineral regulation

Masanobu Kawai
Department of Bone and Mineral Research, Research Institute, Osaka; Women’s and Children’s Hospital, Osaka, Japan.

The circadian clock network is an evolutionally conserved system by which organisms adapt their metabolic activities to the environmental inputs including the availability of nutrients. The master pacemaker of circadian clock system is located in the suprachiasmatic nucleus (SCN) and is well known to play pivotal roles in metabolic regulations including skeletal and mineral metabolisms. In addition to the central pacemaker, peripheral tissues also possess its own circadian system and synchronize with central clock system through hormonal and neuronal signals. Importantly, peripheral circadian system is entrained by external cues such as food availability independent of central regulation. The organisms take advantage of this system to allow for the predictable time-of-day dependent utilization of ingested nutrients by optimizing the metabolic processes of nutrients in peripheral tissues. These findings suggest that circadian regulation of nutrients metabolism is a nodal point connecting nutrient and tissue metabolism. Among the nutrients, calcium and phosphate are the critical components for skeletal metabolism and circulating calcium/phosphate levels have been shown to have circadian profiles in humans, suggesting that mineral metabolism is under the regulation of circadian clock system and disruption of which may affect skeletal homeostasis; however, this has not been well investigated so far. In this talk, I would like to present the current findings how calcium and phosphate metabolism is regulated by circadian clock network and its influences on bone metabolism.

Disclosure

The authors declared no competing interests.

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IS12

Orthopaedic management of osteogenesis imperfecta in the bisphosphonate era

François Fassier
Montreal, Canada.

I. History

II. How the bisphosphonates changed the management plan?

In babies No need to rod non walking children
In toddlers More Upper extremity surgeries
Long-term problems: Risk of delayed non-union:
Several measures were introduced to limit the risk (no Bisphosphonates 48 hours pre-op, and 4 months post-op) as well as technical adjustments.
The duration of the post-op immobilization is still debated

III. Treatment of fractures

Same as in normal bone. The bone is abnormal, but the healing time is normal, therefore, it is illogical to immobilize an OI bone longer than a normal bone.
Bisphosphonates affects osteotomy healing, but not fracture healing, the medication is not stopped.

IV. Lower extremity surgery in OI (hip excepted)

Long bone rodding remains the accepted standard treatment for the correction of deformities. The use of plate and screws must be avoided (stress riser/risk of fracture).
WHAT TYPE OF ROD?
Static rods (K-wires, Rush rods, elastic rods) have the advantage of being easily available, cheap and relatively easy to use.
Telescopic rods (Dubow-Bailey, Sheffield rod or Fassier-Duval) are more expensive but more difficult to insert. Advantages: The re-operation rates is lower with telescopic rods than with static rods. No need for knee or ankle arthrotomies with FD rods.
WHEN TO ROD LOWER EXTREMITIES?
When the child is ready to pull up to stand AND the bone (tibia/femur) is bowed more than 200, or after the 2nd fracture of the same bone the same year.
HOW TO PLAN LOWER EXTREMITY RODDING?
Ideally: rod a femur first and then homolateral tibia under tourniquet. The second side is operated 1 or 2 weeks later.
RESULTS
Functional results of femoral FD rodding in patients receiving bisphosphonates and post-op rehab show improvement of ambulation beyond physiological gain.

V. Specific Hip Problems

1) Femoral neck fractures
2 Coxa Vara
2) Protrusio Acetabuli
3) OI and DDH

VI. Upper Extremity

The problem is not purely cosmetic!
Medical treatment improves UE function.
Forearm rodding leads to a more significant functional improvement than humeral rodding.

VII. Advantages/limitations of Multidisciplinary Approach

Disclosure
Royalties from PegaMedical.
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IS13

Craniosynostoses in rare skeletal disorders
Federico Di Rocco
Reference Center for Rare Disorders, Department of Pediatric Neurosurgery, Hôpital Femme Mère Enfant, Université de Lyon, France.

Craniosynostosis, defined as the premature closure of one or more of the cranial sutures, is a rare disease. It can be isolated or associated to some craniofacial syndromes. In some instances the craniosynostosis can be secondary to specific skeletal disorders such as hypophosphatemic rickets, hypophosphatasia, achondroplasia, mucopolysaccharidosis, osteopetrosis etc. In this evenience, the consequences of the craniosynostosis can be extremely variable depending on the underlying disease as well as on the impact of the altered growth of the skull on the intracranial content. In severe forms, the patient may present with a raised intracranial pressure with its known risks of neurocognitive and visual impairment and possible development of a Chiari malformation and syringomyelia. Differently from the primitive forms of craniosynostosis, the diagnosis of secondary craniosynostosis and of its associated complications may be underestimated in skeletal disorders when based on the merely clinical basis, thus ophthalmological and radiological studies should be considered in such patients. Only the careful observation and follow-up by a multispecialized team of experts in metabolic diseases and in the management of craniosynostosis may assure the correct clinical evaluation and establish the early and appropriate surgical indication in selected cases. Indeed, as for the more common form of craniosynostosis also the premature fusion of the cranial sutures associated to skeletal disorders may in fact result in neurological complications when recognized and treated too late.
Disclosure
The author declared no competing interests.
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IS14

Orthopedic needs in X-linked hypophosphatemic rickets
Rudolf Ganger, C Radler & Rudolf Ganger
Department of Pediatric Orthopaedics and Adult Foot and Ankle Surgery Orthopaedic Hospital Speising, Vienna, Austria.

To point out common patterns of malalignment and deformity in hypophosphatemic rickets and describe treatment principles and techniques as well as common obstacles.
Methods
Deformities of the lower limb in hypophosphatemic rickets do not resolve spontaneously under metabolic control of the disease. To prevent severe deformity and joint overload in the growing child guided growth has been shown to be effective in most cases. As recurrence of malalignment is common during growth, postponing surgical correction with osteotomies until or close to skeletal maturity has been recommended.
Results
The most common deformities in hypophosphatemic rickets are femur and tibia vara combined with an internal torsion deformity of the tibia. Valgus deformity is less common followed by rare cases presenting with unilateral varus-valgus (windswept deformity). Most patients present with disproportionate shortening. Acute correction of the deformities is possible. However, acute shortening for axial correction is necessary in case of severe bowing of the bone due to the relative lengthening of soft tissue (nerves/vessels) on the concave side of the bone. Additional torsional deformities of the tibia can be corrected using six-axis external fixation frames. In previously untreated cases with severe varus and torsional deformity we prefer to correct the legs sequentially using a six-axis frame on the femur and a bi-level six-axis frame on the tibia to restore full anatomic alignment and torsion in one step. At the time of frame removal rushpins can be used to protect the newly formed bone.
Conclusion
Guided growth might be repeatedly used until skeletal maturity to prevent severe deformity and joint over-load. After maturity six-axis frames allow for accurate correction of the most severe multiplanar and multiapical deformities. Less severe deformities and shortening can be corrected successfully with plates or lengthening nails.
Disclosure
Consultant Smith & Nephew Company; Consultant NuVasive Company.
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IS15

Diagnosis of bone dysplasia
Valérie Cormier-Daire
Paris, France.

Abstract unavailable.

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IS16

Current care and new therapeutic approaches to achondroplasia
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Achondroplasia is the most common form of short-limbed dwarfism with a frequency of 1 in 10,000 to 30,000 births. Although it can be inherited in a autosomal dominant manner, 80% of the cases are sporadic. Achondroplasia is classified as one of the FGFR3 chondrodysplasias and more than 97% occur from an activating mutation at residue 380 (p.R380G) of the FGFR3 gene. Current treatment of achondroplasia is mainly directed at prevention and treatment of its complications (obstructive sleep apnea, foramen magnum stenosis, kyphosis, lordosis, genu varum, lumbar spinal stenosis etc.) and involves symptomatic management, surgical intervention, and lifelong follow-up. Short stature is another major problem. Although it is a demanding process, surgical limb lengthening can achieve substantial height enhancement. Growth hormone has been shown to increase adult height +2.8 to 3.2 cm in females and +3.5 to 7.0 cm in males according to Japanese observational studies. The effect is modest, but it will serve as a benchmark for treatments under investigation. Since achondroplasia occurs from activation of FGFR3, which in turn decreases chondrocyte proliferation and differentiation, current nonsurgical strategies are aimed at either directly blocking FGFR3 activation or regulating other signaling pathways that control these cells. Some of the therapies aimed at FGFR3 signaling are tyrosine kinase inhibitors, FGFR3-specific monoclonal antibodies that target the extracellular domain to block ligand binding, and soluble decoy receptors or aptamers that can bind and sequester FGFs. Examples of therapies targeting non-FGFR3 signaling pathways are PTH/PTHrP, meclozine, statins, and CNP. At present, the most promising is the stabilized CNP analog vosoritide since it enhances long bone growth as well as flattens the skull in achondroplasia model mice. The drug is currently undergoing Phase 2 and 3 clinical trials. Recent studies have suggested mTOR and CREB as signaling molecules downstream of FGFR3 and CNP, respectively. Further studies of signaling pathways downstream of or those that interact with FGFR3 will likely lead to new therapeutic strategies not only for skeletal growth but also for other complications of FGFR3 chondrodysplasias.
Disclosure
Biomarin: consultation fee, Novo Nordisk: consultation fee, Lilly: speaker's bureau.
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IS17

TGF-beta inhibition in osteogenesis imperfecta

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Osteogenesis Imperfecta (OI) is characterized by low bone mass, reduced bone strength and fractures. About 90% of OI cases are caused by autosomal dominant mutations in type I collagen (COL1A1 and COL1A2). Recessive OI can be caused by mutations in members of the prolyl-3-hydroxylation complex, including cartilage associated protein (CRTAP), that is important for post-translational collagen modification. The phenotypic overlap between dominant and recessive OI suggests common pathomechanisms. Previously, in bones of mouse models of moderate/severe recessive (Crtap−/−) and dominant OI (G610C OI; glycine substitution in Col1a2), we found an increased signaling of transforming growth factor beta (TGF-β), an important regulator of bone remodeling and bone mass. Interestingly, treatment with the TGF-β-neutralizing antibody 1D11 increased the trabecular bone volume/total volume (BV/TV) in the spine to WT levels in female mice of both models. Moreover, 1D11 increased whole bone strength of femurs of Crtap−/− mice, but did not improve the increased brittleness of the bone material. Together, these findings indicate that dysregulated TGF-β signaling is a common molecular mechanism contributing to the bone defects in these models of recessive and dominant OI. Recently, Tauer and colleagues reported increased TGF-β signaling also in bones of a different model of severe dominant OI with a high incidence of spontaneous fractures (Col1a1Jrt/+ mice with a Col1a1 splice site mutation, leading to an 18 amino acid deletion in Col1a1). In male Col1a1Jrt/+ mice TGF-β inhibition with 1D11 was less effective and lead to only minor trends to higher BV/TV in vertebrae and femurs that were not statistically significant. In summary, these findings demonstrate increased TGF-β signaling in different mouse models of OI; however, the efficacy of pharmacological TGF-β inhibition to improve bone mass may be modulated by the underlying genetic cause and/or severity of OI, as well as mouse gender or genetic background. In OI patients, the safety of TGF-β inhibition is currently tested in a phase 1 clinical trial using Fresolimumab, a human analog of 1D11. The exploratory endpoints may provide additional information regarding the role of OI genotype and severity on the effects of TGF-β inhibition on bone turnover and bone mass.

Disclosure

Anti-TGBβ antibody 1D11 was provided by Genzyme/Sanofi.

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IS18

Anti-resorptive therapy for the treatment of pediatric bone disorders: where do we go from here?

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Intravenous (IV) bisphosphonates (pamidronate, zoledronic acid and neridronate) are the mainstays of medical therapy for numerous pediatric bone diseases. While most frequently prescribed for hypercalcemic disorders and osteoporosis, their potent analgesic effects have also led to their use in fibrous dysplasia, osteonecrosis, sickle cell disease, chronic non-bacterial osteomyelitis, and complex regional pain syndrome. Bisphosphonates given IV are highly effective in preventing incident vertebral fractures in most at-risk patients; their efficacy in stabilizing vertebral dimensions may be attenuated in children with aggressive risk factors and advanced vertebral collapse, highlighting the importance of early vertebral fracture detection. The incidence of long bone fractures is reduced by about 50% in bisphosphonate-treated osteogenesis imperfecta (OI). The lack of a more dramatic fall in incident long bone fractures reflects factors other than cell metabolism in OI, including small bone diameter, limb deformity and that cortical density is less amenable than trabecular density to positive increases. Despite their convenient administration, oral bisphosphonates have shown insufficient efficacy in controlled trials to justify their use first-line in children with osteoporosis; their role as maintenance therapy remains controversial due to lack of sufficient evidence. First-infusion side effects and the burden of IV therapy have opened the door to new approaches. RANKL-targeted denosumab, administered intermittently by sub-cutaneous injection, has received health authority approvals for adult osteoporosis; international pediatric trials in OI and glucocorticoid-induced osteoporosis are underway. In contrast to bisphosphonates, denosumab is short-acting with potential for rebound from osteoclast inhibition, manifesting as reactivation of skeletal resorption, bone density loss and frank hypercalcemia, all of which respond to bisphosphonate therapy. The frequency and extent of the rebound phenomenon in different pediatric settings, along with optimal dosing and frequency of both bisphosphonates and denosumab to achieve clinical endpoints while avoiding over-treatment, merit ongoing study.

Disclosure

Consultant to and participating in clinical trials with Novartis and Amgen.

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Oral Communications

OC1

Association between age at puberty and bone accrual up to 25 years-old

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Objectives
Studies indicate that later puberty is associated with lower bone mineral density (BMD) in childhood. Less is known about effects of puberty timing on long-term bone accrual. We examined association between age at puberty and BMD accrual rate from 10 to 25 years.
Methods
This was a prospective birth cohort of healthy largely European people born in southwest England in 1991–1992 and regularly follow-up from birth to mean age 25 years. Age at puberty was measured by age at peak height velocity (APHV), which was estimated using Super Imposition by Translation and Rotation growth curve modelling of >110,000 repeated height measurements. Whole-body BMD (g/cm^2) was derived from dual-energy x-ray absorptiometry scans at ages 10, 12, 14, 16, 18 and 25 and these repeat measures were used to model BMD accrual. Association between APHV and BMD accrual rate was examined using linear spline models containing interaction terms between APHV and age splines. Models were adjusted for maternal education, birth weight and body mass index at age 7.
Results
We included 6613 participants (50% female) with ~27,000 bone scans. Mean APHV was 13.5 years (standard deviation = 0.9) in males and 11.6 years (standard deviation = 0.8) in females. BMD increased over follow-up, with fastest accrual between 1-year pre-APHV to 2-years post-APHV (males = 0.139 g/cm^2/year (95% confidence interval: 0.127 to 0.151), females = 0.106 g/cm^2/year (0.098 to 0.114)). Per year older APHV was associated with faster but decelerating BMD accrual; the fastest rate was between 14–16 years (males = 0.013 g/cm^2/year (0.011 to 0.015), females = 0.014 g/cm^2/year (0.014 to 0.015)) and the slowest rate between 18–25 years (males = 0.002 g/cm2/year (0.001 to 0.003), females = 0.000 g/cm^2/year (−0.001 to 0.000). Per year older APHV was associated with consistently lower BMD, e.g. at age 14: males = −0.050 g/cm^2 (−0.055 to −0.045), females = −0.044 g/cm^2 (−0.046 to −0.041), and at age 25: males = −0.048 g/cm^2 (−0.052 to −0.044), females = −0.035 g/cm^2 (−0.037 to −0.032). Findings were similar for site specific (including hip) BMD accrual.
Conclusion
Later puberty is associated with persisting lower BMD up to age 25, despite some temporary catch up in BMD accrual during puberty. Advice on how to maximise BMD and minimise its decrease in later life might be particularly important for those with older pubertal age.
Disclosure
The authors declared no competing interests.

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OC2

Adolescent pregnancy and bone density in premenopausal women

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Objectives
High prevalence (20%) of adolescent pregnancy (AP) (1) is observed in India. Reports suggest that pregnancy during adolescence may have deleterious effects on peak bone mass (2). Few reports have described the long-term effects of history of AP on bone. The objective of this study was to compare bone density and geometry of premenopausal women having delivered first child during adolescence (before age of 19 years) or after 19 years.
Methods
A cross-sectional study was conducted in 242 women (aged 28–54.5 years) from Pune, India (November-2015 - November-2017). Women were divided into 2-groups: Group-1: women who had 1st pregnancy before 19-years of age (adolescent pregnancy-AP) (n = 131) and Group-II: women who had 1st pregnancy after 20-years of age (non-AP) (n = 111). Demographic data, anthropometric measurements and biochemical tests were performed using standard protocols. Physical activity and nutrient intakes were recorded using standardised questionnaires. Bone mineral density and bone geometry were measured using iDXA (Lunar iDXA, GE Healthcare) and pQCT (XCT2000, Stratec Inc.).
Results
Mean age of the study group was 37 ± 4.6 years. Group I women (age at first delivery 17 ± 1.6 yrs) were compared to group II women (22.6 ± 3.1 years). Socio-economic status and physical activity during adolescence and at time of measurement were similar in the groups. Both groups were similar in BMI, calcium intake, physical-activity, 25 (OH)D and PTH concentrations (P > 0.1). DXA measured femoral neck bone density in group I was higher (0.908 ± 0.1 vs 0.878 ± 0.1 g/cm^2, (P < 0.05)). pQCT measurements indicated that cortical thickness at radius in Group I (1.99 ± 0.49 mm) was significantly higher than in group II (1.89 ± 0.27 mm, P < 0.05) as was the periosteal circumference (38.03 ± 3.57 mm vs 36.64 ± 2.49 mm, respectively) and total bone area (247.8 ± 34.2 vs 232.7 ± 28.7 mm^2 respectively). Thus, Group I women had wider bones.
Conclusion
Our data suggest that women who had adolescent pregnancies had wider bones with increase in periosteal bone deposition and bone area. We speculate that increase in pregnancy induced higher levels of estrogens during adolescence may have rendered the bones more sensitive to loading.
Disclosure
The authors declared no competing interests.

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OC3

Osteocyte lacunae characteristics in healthy children

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Objectives
Osteocytes play a major role in bone metabolism as mechanosensors, key regulators of osteoblast and osteoclast activity and of the mineral homeostasis. Therefore the assessment of osteocytes characteristics is important to understand bone pathology. We propose to study indirectly the osteocytes by performing quantitative backscattered electron imaging to quantify the sectioned osteocyte lacunae density and size in 2D on bone samples.
Methods
We analysed cortical and cancellous area of transiliac bone biopsy samples from healthy children (n = 6; age range from 2 to 9.4 years). Calcium concentration images (pixel resolution 0.9 μm) were obtained by quantitative backscattered electron imaging (Field Emission SEM Supra40, Zeiss, Oberkochen, Germany). Grey-level (value corresponding to 5.2 weight% calcium content) and size (range of 1.55 μm^2 to 80 μm^2) thresholds were used to obtain binary images of osteocyte lacunae sections (OLS). We measured OLS-density, OLS-porosity and the average value resulting from the frequency distribution of OLS area, perimeter and aspect ratio between major and minor axes (AR).
Results
The OLS-porosity was higher in cortical bone compared to trabecular bone (+24%, P = 0.03). It was due to a higher OLS- density (+33%, P = 0.03). In contrast there was a trend to smaller osteocyte lacunae in cortical bone (OLS-Area: −6%, ns; OLS-Perimeter: −5%, ns). In general, the size distribution analysis revealed less OLS with large size in cortical bone (60–70 μm^2 area range: −50%, P = 0.03; 35–40 μm perimeter range: −28%, P = 0.03). The aspect ratio were similar in both bone regions.
Conclusion
Quantitative backscattered electron imaging is sensitive enough to reveal different osteocyte lacunae section density and size between cortical and trabecular bone. This measurement in a healthy children cohort will serve as reference to characterize bone pathologies in children.
Disclosure
The authors declared no competing interests.

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OC4

Early life vitamin D depletion and mechanical loading determine methylation changes in the RXRA, Runx2 and osterix promoters in mice

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Objectives
Maternal vitamin D status in pregnancy is associated with neonatal bone mass, and altered DNA methylation. Mice exposed to early life vitamin D deficiency have lower bone mass and reduced bone accrual in response to mechanical loading. Using tibias from these mice we assessed DNA methylation of promoters of genetic loci important for bone growth and development.
Methods
C57/BL6 mice received a vitamin D replete or deplete diet for 6 weeks periconceptionally until weaning of offspring at 3 weeks. Non-invasive tibial axial loading with a peak 11N dynamic load was applied to offsprings' left tibiae 3x weekly for 2 weeks at age 8 and 16 weeks. Tibias were collected at 18 weeks and mechanically crushed in liquid nitrogen. DNA was extracted from bone powder using the QiAMP DNA mini kit, and 1ug DNA was bisulfite converted using the EZ DNA methylation kit. Bisulfite pyrosequencing was used to measure DNA methylation of individual CpGs at single base pair resolution within the promoters of Retinoid X receptor (RXRA), Vitamin D receptor, Osterix and Runx2 in loaded and non-loaded tibias. Independent t-tests were used to compare the effect of treatment and/or loading on CpG methylation.
Results
'Deplete' vs 'Replete' groups
In non-loaded tibias, DNA methylation was lower at CpG site −2148 (wrt the transcription start site) in the Runx2 promoter (mean difference −3.44%, 95% CI −0.27 to −6.61, $P=0.036$).
'Deplete' group only
In loaded (vs non-loaded) tibias, DNA methylation was lower at CpG −396 in the Osterix promoter (mean difference −1.54%, 95% CI −0.12 to −2.96, $P=0.037$), and at CpG site −503 in the RXRA promoter (mean difference −4.75%, 95% CI −8.80 to 0.69, $P=0.026$).
'Replete' group only
There was no change in RXRA methylation status at CpG site −503 in the early life vitamin D 'replete' group with loading.
Discussion
These data suggest Vitamin D deficiency induces persistent epigenetic changes at specific gene loci within RUNX2 and Osterix in the offspring. Mechanical loading induced very dynamic changes in DNA methylation within RXRA. Epigenetic mechanisms may contribute to early life nutritional programming of bone mass and the response to mechanical loading.
Disclosure
NJB consults for Alexion, Mereo, UCB and Amgen, and receives grant support for clinical studies from Alexion and Amgen.

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OC5

Low birthweight is associated with poorer limb muscle mass and grip strength in middle age: findings from the UK Biobank Imaging Enhancement

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Objectives
Low birthweight has been shown to be associated with poorer musculoskeletal health in later life in a variety of epidemiological studies. We investigated relationships between birthweight, and grip strength or magnetic resonance imaging (MRI) measures of muscle volume in UK Biobank.
Methods
UK Biobank is a large prospective cohort of men and women aged 40–69 years, including a detailed baseline assessment in which birthweight was collected by self-report. A subset underwent MRI examination with the dual-echo Dixon Vibe protocol, from neck to knees. Automated body composition analysis was performed using the AMRA Profiler™ system, to segment and quantify total thigh muscle volume. Grip strength was assessed using a Jamar hydraulic hand dynamometer. Associations between birthweight, and thigh muscle volume or grip strength (expressed as Fisher-Yates z-scores) were investigated using multivariate linear regression analysis. This study was conducted under generic ethics approval (NRES:11/NW/0382).
Results
3699 participants [1513 men, mean (S.D.) age 61.0 (7.6) years and 2186 women, age 60.1 (7.4) years] were able to recall their birthweight and had their grip strength assessed or underwent MRI body composition analysis. In both men and women, higher birthweight was associated with greater thigh muscle volume (adjusted for age and body mass index (BMI)): men, β (95% CI): 0.229 (0.156, 0.301) S.D./kg, $P<0.001$; women, β (95% CI): 0.284 (0.221, 0.346) S.D./kg, $P<0.001$. Higher birthweight was also associated with higher grip strength (adjusted for age and height); men, β (95% CI): 0.123 (0.051, 0.195) S.D./kg, $P=0.001$; women, β (95% CI): 0.070 (0.007, 0.134) S.D./kg, $P=0.031$. Apart from the association with grip strength in women, these associations persisted after additional adjustment for current smoking and physical activity.
Conclusion
Birthweight was positively associated with MRI measures of thigh muscle volume and grip strength in a population of middle-aged UK adults. These findings provide novel evidence in support of the developmental programming hypothesis and suggest that interventions to optimise birthweight may help to prevent sarcopenia and reduce the risk of falls in future generations.
(Project 3593)
Disclosure
The authors declared no competing interests.

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OC6

Anthropometric characteristics of pediatric patients with hypophosphatasia: data from the Global Hypophosphatasia Patient Registry

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Objectives
Limited data exist on growth parameters in children with hypophosphatasia (HPP), a rare metabolic disease characterized by impaired bone mineralization. We aimed to describe growth characteristics in untreated children with HPP enrolled in the Global HPP Patient Registry.
Methods
Children (<18 years old) with a diagnosis of HPP who were not receiving enzyme replacement therapy with asfotase alfa at the time of evaluation were identified from the registry, and data on their clinical characteristics and first and last available growth assessments, including height and weight (prior to treatment if previously treated), were extracted. Median (min, max) z-scores were calculated using World Health Organization and Centers for Disease Control and Prevention standards.
Results
Of the 194 children (59% female) included, median (min, max) age at first HPP manifestation was 1.1 (–0.5, 16.9) years ($n=161$). The most common first clinical HPP manifestations were premature loss of deciduous teeth (52% of patients), bone deformities (32%) and failure to thrive (21%); 53% of patients had experienced ≥3 clinical HPP manifestations and 48% had manifestations in ≥3 organ systems. Of the patients born full term (92% of patients with data), height

z-score at first assessment was –0.2 (–6.3, 3.2), with 18% of patients below the third percentile, and weight z-score was 0.0 (–4.1, 7.1), with 8% below the third percentile. For patients aged <2 years at assessment, change in length z-score was –1.2 (–5.1, 2.5) over a median (min, max) of 1.1 (0.0, 2.0) years, whereas height z-score remained relatively consistent in patients aged ≥ 2 years (z-score change 0.0; –6.1, 5.0) over a median of 1.5 (0.0, 16.0) years. For patients born small for gestational age (SGA; $n=13$), height and weight z-scores increased over time, but decreased for patients who were not SGA ($n=109$). Height z-score did not correlate significantly with the number of HPP manifestations experienced.

Conclusion

These data suggest growth worsens over time in patients aged <2 years but remains relatively unchanged for those ≥ 2 years. Furthermore, height may not be predictive of disease severity in children.

Disclosure

Wolfgang Högler, Agnès Linglart, Priya Kishnani, Lothar Seefried, Cheryl Rockman-Greenberg, Keiichi Ozono and Gabriel Ángel Martos-Moreno are consultants for, and have received research funding and honoraria from, Alexion Pharmaceuticals, Inc. Anna Petryk and Shona Fang are employees of, and may own stock/options in, Alexion Pharmaceuticals, Inc., which sponsored the study.

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OC7

Comparison of zoledronate and pamidronate in children with skeletal disorders: Short term safety experience from a single institution

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Objectives

Bisphosphonates are frequently used in children with skeletal disorders, however optimal dosing and regimens are unknown. Early treatment focused on pamidronate (PAM), a second-generation formulation, however use of zoledronate (ZOL), a more potent third-generation bisphosphonate, has recently increased due to shorter and less frequent infusions. The objective of this study is to compare short-term safety of ZOL and PAM in a pediatric population.

Methods

We performed a ten year retrospective chart review including demographics, indications for treatment, and bisphosphonate used. Adverse events (AEs) for 7 days post-infusion were categorized: i) Acute phase reactions (APR): fever, bone pain, myalgia, decreased oral intake, and/or fatigue; ii) nausea/vomiting; iii) hypocalcemia (serum calcium <8.5 mg/dl); iv) seizures; v) respiratory distress; vi) anaphylaxis; vii) emergency department evaluations and hospital admissions.

Results

119 patients (median age 8.6y, range 0.1–23.4) received 782 infusions (46 ZOL, 736 PAM) between June 2007 and August 2017. The most common diagnoses were osteogenesis imperfecta (31%), cerebral palsy (22%), and muscular dystrophy (12%). AEs were more common after ZOL than PAM: 50% vs 23.1% for initial infusions, $P=0.03$; and 18.8% vs 4.5% for subsequent infusions, $P=0.0004$. APRs occurred after 6/46 total ZOL infusions (13.0%) vs 28/736 total PAM infusions (3.8%) ($P=0.003$). Nausea/vomiting occurred after 4/46 ZOL (8.7%) vs 20/736 PAM infusions (2.7%) ($P=0.02$). Hypocalcemia occurred after 5/46 ZOL (10.8%) vs 4/736 PAM infusions (0.5%) ($P<0.0001$), and was managed with oral calcium and calcitriol. An increase over baseline seizure activity was reported after 2/46 ZOL (4.3%) vs 1/736 PAM infusions ($P<0.0001$). Respiratory distress occurred after 0/46 ZOL and 2/736 PAM infusions ($P=0.72$) There were no cases of anaphylaxis. Emergency department evaluations and/or admissions occurred after 2/46 ZOL (4.3%) and 4/736 PAM infusions (0.5%) ($P=0.04$).

Conclusion

ZOL treatment is associated with a higher incidence of AEs compared to PAM, consistent with its greater potency. While AEs following both ZOL and PAM are common, they are generally mild and treatable. Additional research regarding long-term safety, efficacy, and cost are needed to determine if ZOL's convenience justifies its routine use over PAM.

Disclosure

The authors declared no competing interests.

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OC8

Bisphosphonate improves hip range of motion and pain but not femoral head sphericity: A multicentre, randomized clinical trial of children with Perthes disease

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Introduction

Perthes disease (PD), idiopathic femoral head avascular necrosis, often results in deformity. The underlying cause is unclear and long-term function is directly related to the roundness of femoral head. Current treatment include mechanical treatments and various surgical procedures, which are therapeutic but can't prevent collapse. A multicentre, prospective, randomised controlled trial of 12 months zoledronic acid (ZA) in children with PD was conducted. We hypothesized that by inhibiting osteoclastic resorption, ZA could maintain femoral head strength and shape at 24 months.

Methods

Inclusion criteria were >5 y/o, acute onset and unilateral PD. The primary outcome measure was deformity index (DI) at 24 months. Secondary outcome measures were femoral head subluxation (extrusion index), FACES pain scale, non-arthritic hip score (NAHS) and Global Paediatric Outcome Data collection instrument (PODCI). The patients were randomised into two treatment arms: a) Standard care or b) Zoledronic acid and standard care. Safety parameters included bone densitometry (DXA) and mineral homeostasis.

Results

Seventy-eight patients (mean age $7.84y \pm 1.64$) were evaluated. At 12 months, DI measurements on pelvic radiograph showed no difference between the two groups. All participants showed significant improvement of range of motion over 2 years ($P<0.05$), but was comparable between groups. Patients in the treatment group reported better pain relief as evidenced by FACES pain scale and the pain component of PODCI ($P<0.05$). DXA results revealed significant increment following 12 month of ZA. Following completion of trial at 24 months, DI measurements again showed no difference ($P=0.54$). The same findings were found for extrusion index ($P=0.82$). Hip range improved further, with significantly improved abduction in the treatment group ($P<0.05$). However, hip pain was no longer significantly decreased at this juncture. Otherwise, biochemical markers of bone turnover were within normal range. There were no reports of fracture, spondylolisthesis or osteonecrosis of jaw.

Conclusion

Bone density was significantly increased following treatment with ZA, although within the reported range in previous studies. With this clinically-safe dosage, the treatment of children with PD utilizing ZA may provide early pain relief and subsequent improvement in hip range of motion, but does not prevent femoral head deformity.

Disclosure

Partial funding for study from Novartis.

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OC9

Efficacy and safety of intravenous zoledronic acid for the treatment of pediatric glucocorticoid-induced osteoporosis: An international, randomized placebo-controlled trial

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Objectives
We evaluated the efficacy and safety of intravenous zoledronic acid (IV ZA) in children with glucocorticoid-induced osteoporosis (GIOP) through a randomized, placebo (PBO)-controlled trial.
Methods
In this multi-national Phase 3 trial (NCT00799266), children 5–17 years of age with GIOP and low-trauma vertebral fractures (VF) were randomized 1:1 to IV ZA 0.05 mg/kg or IV PBO every six months for one year. Changes in lumbar spine areal bone mineral density Z-scores (BMDZ, primary outcome) and the frequency of new low-trauma VF were assessed centrally with treatment blinding. Adverse events (AEs) and serious AEs (SAEs) were recorded.
Results
Thirty-four children (38% with Duchenne, 35% rheumatic conditions, 27% Crohn's disease, mean age 12.6 ± 3.4 years, 68% boys) were enrolled in the study (ZA, $n=18$; PBO, $n=16$). Thirty-three and 30 children completed 6 and 12 months of the trial, respectively; two children (ZA) withdrew for logistical reasons (school commitments, participation in another trial), and two withdrew after incident fractures (clavicle, ZA; new VF, PBO). Data are presented on 33 children with at least one follow-up visit. The mean $\pm$ standard deviation change in spine BMDZ over 1 year was -2.1 ± 0.8 to -1.5 ± 1.0 on ZA compared with -2.4 ± 0.9 to -2.3 ± 1.0 on PBO, least squares (LS) mean between-group BMDZ difference 0.414, 95% confidence interval 0.022, 0.806; $P=0.039$. Two children on PBO had new low-trauma VF in previously normal vertebrae. Eight-three percent of children had AEs on ZA vs 75% on PBO. Sixty-seven percent (ZA) vs 25% (PBO) of AEs occurred within 10 days following the first infusion, largely due to transient post-dose gastrointestinal complaints. Five children on ZA and one child on PBO had SAEs; 4/5 children on ZA had gastrointestinal SAEs, and two of these children had SAEs within 10 days following ZA (transient, one with hypocalcemia, one with acute phase reaction symptoms). There were no deaths, nor treatment discontinuations due to ZA.
Conclusions
Over one year, spine BMDZ in children with GIOP significantly increased on ZA compared with PBO. AEs and SAEs were consistent with the known, transient side effects of ZA.
Disclosure
Dr. Ward has been a consultant to Novartis Pharmaceuticals. The other co-authors have nothing to declare.
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OC10

Next-generation antibody-guided enzyme replacement therapy for lysosomal storage diseases

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Objectives
Lysosomal diseases (LDs) are a heterogenous group of 40+ genetic disorders that can affect virtually all organs and systems, including the skeletal system. They are often caused by the loss of an enzyme critical for the breakdown of macromolecules in the lysosome, leading to accumulation of these substrates and subsequent lysosomal dysfunction. Enzyme replacement therapy (ERT) is the primary treatment option for many LDs, but several issues hinder the efficacy of this therapy. Poor delivery of replacement enzyme to key tissues – notably skeletal muscle, cartilage, and bone – leaves critical organs undertreated. Additionally, many recombinant enzymes are immunogenic, and due to difficulties delivering ERT by infusion patients may not be getting enough recombinant enzyme to get full benefits. Our goal is to develop an approach to address all these key issues.
Methods
Here, we present an antibody-guided enzyme replacement therapy approach wherein antibodies are fused to replacement enzyme. The antibody portion of the molecule guides the enzyme to critical tissues by targeting cell-surface internalizing proteins. The targeted internalizing proteins are chosen based on their superior expression and kinetics compared to the endogenous uptake receptors. By combining this approach with gene therapy, we can also address immunogenicity and delivery issues.
Results
In the Pompe disease model mice, where loss of acid alpha-glucosidase (GAA) causes glycogen accumulation in muscles, we show that antibodies against broadly-expressed or skeletal muscle-specific internalizers fused to hGAA (antibody::GAA) were able re-direct GAA independently of the endogenous uptake receptor *in vitro* and in vivo. By further combining this approach with gene-therapy delivery, we showed that a single dose of an AAV antibody::GAA cleared glycogen in cardiac and skeletal muscles in Pompe mice to wild-type levels, while AAV GAA was only able to reduce 50% of muscle glycogen at the same dose. We further show that downstream markers of disease in these mice, such as elevated autophagy and reduced grip strength were rescued in the AAV antibody::GAA treated mice.
Conclusions
AAV-delivered antibody-guided ERT shows promise in the mouse model of Pompe disease and may be generalizable to other lysosomal storage diseases, including those affecting bone and cartilage.
Disclosure
The authors are employees of Regeneron Pharmaceuticals.
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OC11

Targeting adeno-associated viral vectors to fractures and the skeleton

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Objectives
While local gene therapy for bone applications has shown some success in preclinical models, systemic delivery of transgenes to the skeleton remains a considerable challenge. Viral vectors such as adeno-associated viruses (AAVs) have great potential as vectors for systemic transgene delivery and may be adapted for emerging gene editing technologies. Furthermore, AAV vectors can have high efficiency, low immunogenicity, and selective tropism towards different tissues.
Methods
In this study, we screened 18 natural and engineered recombinant AAV variants. AAVs constitutively expressing Cre-recombinase (under a CAG promoter) were assessed using a murine fracture model using the Ai9 reporter mouse line (Cre-dependent tdTomato expression). AAVs were injected into fractures at time of surgery, and transduction efficiency assessed after two weeks. Transduced osteoblasts were detected using fluorescent alkaline phosphatase staining. Next, a systemic delivery model was performed using tail vein injection, which compared variants AAV2, AAV8, and AAV-DJ. Additionally, Cre expression was restricted using bone cell specific promoters Sp7 and Col2.3. Transduction of bone, and other tissues including brain, heart, lung, liver, spleen and kidney were examined after two weeks.
Results
AAV8, AAV9, and AAV-DJ were able to yield robust tdTomato expression within the healing fracture callus at the study end point. AAV8 and AAV-DJ showed the highest transduction of osteoblastic cells within the callus, which were then used for the systemic delivery. Following tail vein injection, AAV8 was able to transduce cells within the skeleton. Restriction of reporter expression to bone cells was facilitated by constructs utilising the Sp7 and Col2.3 promoters, with Sp7 providing the greatest specificity. At moderate doses (5×10^{11}/mouse or $\sim 2.5 \times 10^{13}$/kg) high levels of tdTomato+ osteoblasts and osteocytes were observed throughout the long bones.
Conclusion
We have identified AAV variants with a high tropism for murine bone cells, and vectors for high efficiency in vivo gene delivery to bone. The AAV8-Sp7-Cre vector has significant practical applications for inducing gene deletion in floxed mouse models in post-natal bone. Future work will validate AAV vectors that enable targeted CRISPR gene editing and deletion that have relevance to the treatment of genetic bone disease.
Disclosure
AS and DL have received funding support from Amgen, Novartis AG, Celgene Corp, and N8 Medical for research unrelated to this study. CJM has received funding support from Alexion, Novartis AG for research unrelated to this study.
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OC12

Combination treatment of a novel activin receptor IIB ligand trap and zoledronate improves muscle and bone proprieties in a mouse model of osteogenesis imperfecta

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Osteogenesis imperfecta (OI) is not only characterized by fragile bones but also impaired muscle mass and function. Inhibition of signaling through the activin receptor IIB has the potential to improve both muscle and bone mass. Here we investigated the effect of a soluble activin receptor IIB ligand, ACE-2494 (10 mg/kg twice a week), in 4-week old Col1a1Jrt/+ male mice, a model of severe dominant OI caused by a Col1a1 splice site mutation. Four weeks of treatment with ACE-2494 alone resulted in a significant gain in muscle mass (quadriceps +42%, tibialis anterior +33%, extensor digitorum longus +46%, soleus +29%, gastrocnemius +15%) and femur length (+5%) compared to vehicle-treated OI mice (all $P<0.001$), but no significant treatment effect was found for bone mass or mechanical properties of the right femur using three-point bending test. We therefore combined ACE-2494 treatment with concomitant intraperitoneal zoledronate injections (0.05 mg/kg three times a week). Compared to ACE-2494 alone, this resulted in increased bone mass (+405% in trabecular BV/TV at the femoral distal metaphysis) and cortical thickness (+42% at the femoral midshaft) (all $P<0.001$). In conclusion, ACE-2494 stimulated growth in muscle mass and bone length. Combination treatment of ACE-2494 with zoledronate in addition increased trabecular and cortical bone mass.

Disclosure

Dr Frank Rauch: PreciThera Inc: Study grant to institution.

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OC13

Analysis of osteogenesis imperfecta in pathology and the effects of 4-phenylbutyric acid using patient-derived fibroblasts and induced pluripotent stem cells

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Objectives

Osteogenesis Imperfecta (OI) is a heritable brittle bone disease mainly caused by mutation of COL1A1 or COL1A2. Treatment with bisphosphonate is not effective enough in patients with severe OI. 4-phenylbutyric acid (4-PBA) may become a new medicine, which was reported to ameliorate the phenotype of an OI zebrafish model. In the present study, we aimed to analyze the pathology of OI and the effects of 4-PBA on patient-derived fibroblasts and induced pluripotent stem cells (iPSCs).

Methods

Dermal fibroblasts were obtained from 6 patients with OI: 1 had a nonsense mutation, 2 had a glycine substitution mutation and 3 had an exon skipping mutation in COL1A1 or COL1A2. Endoplasmic reticulum (ER) retention of type I procollagen was observed by immunofluorescent staining. The expression of ER stress markers was quantified by real-time PCR. Protein level and mRNA level of type I collagen were measured by ELISA and real-time PCR, respectively. The molecular weight of secreted type I collagen was analyzed by SDS-PAGE. Post-translational modifications of type I collagen were analyzed by LC-MS. Normal and patient-specific iPSCs were established from fibroblasts, and induced to osteoblasts. Mineralization was assessed by Alizarin Red S staining. We evaluated the effects of 4-PBA on above experiments.

Results

In OI fibroblasts, immunofluorescent staining showed excessive amount of procollagen in ER. 4-PBA addition decreased the retention in a dose-dependent manner. The expression of BIP and CHOP was not changed by 4-PBA. In OI with a glycine substitution, the protein and mRNA levels of type I collagen were increased and canceled by 4-PBA. SDS-PAGE showed the retarded band and LC-MS analysis showed overglycosylation of type I collagen with a glycine substitution. 4-PBA did not change the retarded band, but partially improved overglycosylation. Osteoblasts differentiated from patient-specific iPSCs exhibited less calcification than normal, and 4-PBA improved the capability of calcification to the normal level.

Conclusion

4-PBA decreased the excessive production and accumulation of type I collagen in OI fibroblasts, and partially improved overglycosylation. In addition, 4-PBA improved mineralization of osteoblasts differentiated from patient-derived iPSCs. Since 4-PBA has already been approved for other disease, we may reposition 4-PBA for OI.

Disclosure

The authors declared no competing interests.

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OC14

Burosumab resulted in greater improvement in clinical outcomes than continuation with conventional therapy in younger (1-4 years-old) and older (5-12 years-old) children with X-linked hypophosphatemia

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Objective

We compared the efficacy and safety of burosumab, a monoclonal antibody against FGF23, to conventional therapy [oral phosphate and active vitamin D (Pi/D)] in children with X-linked hypophosphatemia (XLH).

Methods

In this Phase 3 trial (NCT02915705), 61 children with XLH (1-12 years-old) were randomized 1:1 after a 7-day Pi/D washout to receive burosumab starting at 0.8 mg/kg SC Q2W or reinitiate Pi/D optimally titrated by investigators. Eligibility criteria included Rickets Severity Score $\geq$2.0 despite prior Pi/D treatment. Healing of rickets (primary endpoint) was assessed by radiologists blinded to treatment using the Radiographic Global Impression of Change (RGI-C) at Week 40. Lower limb deformity and growth were assessed at Week 64. In addition to comparing all subjects, we compared treatments in subjects $<$ and $\geq$5 years-old.

Results

By Week 40, RGI-C was significantly higher with burosumab than with Pi/D (LS mean$\pm$SE: burosumab, $+1.9\pm0.1$ vs Pi/D$+0.8\pm0.1$; $P<0.0001$); RGI-C results were similar in subjects $<$5 years-old (burosumab, N$=$14, $+1.9\pm0.2$ versus Pi/D, N$=$12, $+0.7\pm0.2$) and $\geq$5 years-old (burosumab, N$=$15, $+2.0\pm0.1$ versus Pi/D, N$=$20, $+0.9\pm0.1$). Improvement in lower limb deformity score was greater with burosumab than Pi/D for all subjects (Week 64 LS mean$\pm$SE: $+1.3\pm0.2$ vs $+0.3\pm0.1$; $P<0.0001$), subjects $<$5 years-old ($+1.5\pm0.3$ vs $+0.5\pm0.2$), and subjects $\geq$5 years-old ($+1.0\pm0.2$ vs $+0.1\pm0.1$). Burosumab showed greater improvement than Pi/D in length/height Z-score for all subjects (Week 64 LS mean change$\pm$SE: $+0.17\pm0.07$ vs $+0.02\pm0.04$; $P=0.0490$), subjects $<$5 years-old ($+0.15\pm0.12$ vs -0.05$\pm$0.07), and subjects $\geq$5 years-old ($+0.17\pm0.05$ vs $+0.08\pm0.04$). Dental adverse events (AEs) and AEs of interest, including hypersensitivity and injection site reactions, were more frequent with burosumab, and were mild to moderate in severity overall. Three serious AEs occurred per group, all unrelated to treatment and resolved. No discontinuations occurred.

Conclusions

Both younger and older children with XLH demonstrated greater improvements in rickets, bowing, and growth after burosumab than those who continued with Pi/D.

Disclosure

LW, EI, MW, CM, AP, WH, JS, RP, NN, HC, ON, and FG served as clinical investigators for this study sponsored by Ultragenyx Pharmaceutical Inc. MM, AS, C-YC, and JSM are employees and shareholders of Ultragenyx Pharmaceutical Inc.

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OC15

Sustained efficacy and safety of burosumab, a fully human anti-FGF23 monoclonal antibody, in children and early adolescents with X-linked hypophosphatemia

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Objective
We evaluated the long-term efficacy of burosumab, a monoclonal antibody against FGF23, in a Phase 2 Study (NCT02163577) in children with XLH.
Methods
Fifty-two children with XLH (5-12 years-old, Tanner $\leq$ 2) were randomized 1:1 to receive subcutaneous burosumab Q2W or Q4W for 64 weeks. Doses were titrated up to 2 mg/kg/dose targeting serum phosphorus levels within 1.1–1.6 mmol/l. All subjects entered the long-term extension at Week 64, in which Q4W-treated subjects changed to Q2W; treatment continued through Week 88. Data through Week 160 will be available at the time of presentation. The significant improvements in rickets severity observed with the Radiographic Global Impression of Change (RGI-C) at Week 64 (LS mean $\pm$ SE: Q2W + 1.56 $\pm$ 0.11, Q4W + 1.58 $\pm$ 0.11) were maintained through Week 88 (Q2W + 1.67 $\pm$ 0.14, Q4W $\rightarrow$ Q2W + 1.85 $\pm$ 0.09). Thirteen (50%) and 16 (62%) Q4W $\rightarrow$ Q2W subjects had a RGI-C $\geq$ +2.0 by Week 64 and 88, respectively. Improvements observed at Week 64 in height Z-score (LS mean change $\pm$ SE: Q2W + 0.19 $\pm$ 0.05, Q4W + 0.12 $\pm$ 0.06) and the 6-Minute Walk Test (Q2W + 53 $\pm$ 9 meters, Q4W + 41 $\pm$ 10 meters) were sustained through Week 88 (height Z-score: Q2W + 0.26 $\pm$ 0.05, Q4W $\rightarrow$ Q2W + 0.15 $\pm$ 0.06; 6MWT: Q2W + 65 $\pm$ 11 meters, Q4W $\rightarrow$ Q2W + 44 $\pm$ 12 meters). Significant increases in serum phosphorus were maintained through Week 88 (mean [SD] mmol/l: Q2W 1.1 [0.1]; Q4W $\rightarrow$ Q2W 1.1 [0.1]). For the 9 subjects who transitioned into adolescence (ranging from $\sim$12 years-old at baseline to $\sim$14 years-old at Week 88), improvements in serum phosphorus and rickets severity were maintained. One subject had concurrent serious AEs (fever/muscle pain) which resolved within a day. Other AEs were generally mild to moderate in severity; no new serious AEs emerged between Weeks 64–88. No clinically meaningful changes in serum calcium or iPTH occurred. No subject discontinued therapy or developed hyperphosphatemia.
Conclusion
Long-term burosumab treatment maintained improvements in clinical outcomes, including rickets severity, growth, and mobility in children and early adolescents with XLH. Children that changed from the Q4W to Q2W regimen at Week 64 showed additional improvement in rickets severity.
Disclosure
WH, TC, EI, AP, AB, AL, RP, WvH, and MW served as clinical investigators for this study, sponsored by Ultragenyx Pharmaceutical Inc. MM, AS, and JSM are employees and shareholder of Ultragenyx Pharmaceutical Inc.

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OC16

A natural history study of generalized arterial calcification of infancy (GACI) and autosomal recessive hypophosphatemic rickets (ARHR2) due to ENPP1 or ABCC6 deficiency: interim analysis

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Introduction
ENPP1 Deficiency manifests as GACI type 1 in infants, a disorder characterized by extensive arterial calcifications and stenoses, often fatal in utero or in early infancy. Beyond six months, the mortality rate significantly decreases among survivors, who may later develop ARHR2, characterized clinically by short stature, bone deformities and pain. ABCC6 Deficiency also manifests as GACI type 2 in infants and is clinically indistinguishable from GACI type 1. Animal data suggest that enzyme replacement therapy with ENPP1-Fc may prevent the mortality of GACI and morbidity of ARHR2.
Objective
To collect data on 100 patients to characterize the natural history of the disease.
Methods
Two IRB-approved natural history studies at the National Institutes of Health (NCT03478839) and Münster University Children's Hospital (NCT03758534).
Interim Results
Of 42 probands, 37 had GACI (median age at diagnosis 1.2mo), 17 had ARHR2 (median age at diagnosis 72mo). Thirteen probands had both GACI and ARHR2. Of 38 probands with genetic analyses, 29 had ENPP1 mutations and 8 had ABCC6 mutations. In GACI probands, initial symptoms included dyspnea (62%) and cyanosis (16%); 73% were ventilated. Arterial calcification was observed in 87%, presenting between 0.7 and 1.1mo, most commonly in the aorta (88%), coronary (72%), pulmonary (69%), renal (63%) and carotid (60%) arteries. Calcification resolved in 32% (aorta), 40% (renal) and 44% (coronaries) of cases, at median ages of 13.3, 11.9, and 14.7 months, respectively. Twenty-nine individuals had cardiac dysfunction, with cardiac failure in 16 and myocardial infarction in 6. Joint or organ calcification was present in 49% and 62%, respectively. In probands with ARHR2, 71% had pain, 53% had bowing, and 29% had short stature. Probands over 1-year old with ENPP1-deficiency developed rickets in 68% (13/19). 60% of GACI-patients were treated with bisphosphonates. Overall mortality for the GACI-cohort was 38% (14/37 patients, median age 1.2 months). Mortality rates in the bisphosphonate-treated vs. untreated sub-cohorts was 18% and 44%, respectively.
Conclusion
The natural history of GACI and ARHR2 shows significant mortality and morbidity indicating the need for better treatments. More understanding is needed prior to clinical trials; the current study aims to address this knowledge gap.
Disclosure
Grant support and consulting fees from Inozyme Pharma.

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OC17

Growth curves for children with X-linked hypophosphatemia

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Objective
We constructed height growth curves for children with XLH from birth to early adolescence, a majority of whom received conventional therapy consisting of multiple daily doses of oral phosphate and active vitamin D.
Methods
Growth data from four clinical studies were pooled to construct the growth curves. UX023-CL002 was an observational, retrospective chart review of 103 children with XLH, 1–14 years of age. Pre-treatment data were collected from three remaining clinical studies (each investigating the safety and efficacy of burosumab, a fully human monoclonal antibody against FGF23): a phase 2 trial (UX023 CL201, NCT02163577) in 52 children with XLH ages 5–12 years old at enrollment; a phase 2 trial (UX023 CL205, NCT02750618) in 13 children with XLH, 1–4 years old at enrollment; and a phase 3 trial (UX023-CL301, NCT02915705) in 61 children with XLH, 1–12 years old at enrollment. We constructed height-for-age growth curves including values for the 5th, 10th, 25th, 50th, 75th, 90th and 95th percentiles for these children with XLH, and compared these data to growth curves representing population norms from the CDC (year 2000).
Results
228 patients (132 girls, 96 boys) with 2,381 height measurements were included. Nearly all subjects (>99%) had received conventional therapy before enrollment. For boys at 0.25, 0.50, 0.75, 1.0, and 2.0 years-old, the median height percentile was 46%, 37%, 26%, 18%, and 5% respectively; girls median height percentile was 52%, 37%, 25%, 18%, and 7%, respectively. Compared to the CDC growth curves, height velocity in children with XLH fell below that of healthy children near 1 year of age and progressively declined during early childhood, with all median height percentiles <8% between 2 and 12 years-old.
Conclusion
Though nearly all subjects had received conventional therapy, children with XLH show evidence of decreased height velocity by 1 year of age. XLH growth curves

provide a helpful point of reference to evaluate therapeutic interventions on growth, and in particular will assist with objective evaluations of novel treatment approaches, such as burosumab. Future research will aim to collect additional growth data from these patients to provide complete XLH growth curves through the adolescent years.

Disclosure

Dr. Carpenter and Whyte served as clinical investigators for studies sponsored by Ultragenyx Pharmaceutical. Dr.s Skrinar, Chen, and San Martin are employees and shareholders of Ultragenyx Pharmaceutical.

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OC18

Developing a human-mouse hybrid model of osteogenesis imperfecta for investigating new therapies for children

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Objectives

Osteogenesis imperfecta (OI) displays a heterozygous phenotype even amongst similar genotypes. It has therefore been difficult to establish a mouse model which represents clinical OI in children. By engrafting human OI bone into mice we have developed a hybrid model enabling us to investigate the efficacy of new treatments for this phenotypically diverse condition.

Methods

Bone chips, that would otherwise be discarded, were collected from children with (3) and without (2) OI, undergoing orthopaedic surgery. 10 to 14 bone chips were collected from each participant, each measuring 5mm3. These were grafted subcutaneously onto immune deficient NOD SCID mice. Two bone chips were implanted into each mouse. After 4 weeks, the mice were sacrificed, and the bone chips removed. One bone chip was fixed and sectioned for histomorphology/ immunohistochemistry. The other bone chip was homogenised and RNA extracted. Genetic expression of target pathways were investigated from bone pre and post xenograft to test for genetic stability of bone in the hybrid model.

Results

Human OI and control bone remained alive and metabolically active for the 4-week time period tested. Osteoclasts remained active, as defined by the uptake of TRAP staining and the surrounding lytic areas were visible on histological sections. Osteoblasts were identified on H&E stain. Good quality and quantity RNA was extracted- identified on nanodrop spectrophotometers, 260/280 ratio 1.93 and 260/230 ratio 1.93, count >350 ng/μL. We are currently using microfluidic cards to analyse expression of genes associated with the TGFB pathway in OI and control bone before and after xenotransplantation.

Conclusion

We have generated a human-mouse hybrid model of OI that contains metabolically active human bone, that remains architecturally identical to the original patient sample. The presence of the osteoclasts after 4 weeks suggests successful engraftment of haemopoietic precursors, as well as the presence of osteoblasts expressing RANK- ligand, a necessary factor for osteoclastogenesis. This model may provide a novel method of identifying changes to gene expression, bone microarchitecture and mechanical properties following therapeutic intervention across multiple different patients, allowing for review of heterogeneity to response.

Disclosure

Nick Bishop consults for Alexion, Mereo, UCB and Amgen, and receives grant support for clinical studies from Alexion and Amgen.

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OC19

Altered 3 hydroxylation complex in bone homeostasis

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Objectives

Osteogenesis imperfecta (OI) is a heritable disorder characterized by bone deformity and skeletal fragility. Cartilage associated protein (CRTAP), proline 3-Hydroxylase 1 (P3H1) and Cyclophylin B (PPIB) are components of the endoplasmic reticulum (ER)-resident complex involved in the 3-hydroxylation of specific proline residues in collagen type I α chains. Mutations in these proteins are responsible for recessive OI type VII, VIII and IX, respectively. Murine models for these diseases exist, but our goal was to exploit the availability of zebrafish models to deeper understand the phenotype at early developmental stages and to favour drug screening reducing amount, timing and cost.

Methods

CHOPCHOP was used for guide RNA selection. pT7gRNA vector was used for gRNA subcloning and *in vitro* transcription and the pT3TS-nCas9n plasmid for Cas9 mRNA synthesis. Alizarin red staining, μCT and X-Rays were used for bone characterization. The growth rate of caudal fin was performed by measuring regrown tail after amputation. Collagen type I was characterized by SDS-PAGE. Collagen fibers were analysed by transmission electron microscopy (TEM).

Results

OI type VII and VIII knock out zebrafish models were generated using CRISPR Cas9 system. P3h1 and Crtap mutants are smaller than WT and show a delayed mineralization starting from the first weeks of life. Their phenotype is worsening with age, as observed by the severe skeletal deformities present during adulthood. Bone formation, evaluated on fin regeneration, is delayed in p3h1 mutants compared to WT. Collagen type I is overmodified in both mutants, as suggested by the broadened α bands observed in SDS-PAGE. TEM images show smaller collagen fibers diameters in mutants with respect to WT. An enlargement of ER cisternae is evident in mutants, suggesting the presence of ER stress due to collagen retention.

Conclusion

We proved the goodness of zebrafish model to reproduce the phenotype of recessive OI type VII and VIII. Since ER stress could be a potential therapeutic target, our goal will be to use our models for drug screening in order to pave the way to new pharmacological treatments.

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Disclosure

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OC20

Identifying the role of NBAS in bone fragility using zebrafish and exploring therapeutic targets to reverse NBAS activity

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Background

We discovered that variants in NBAS (Neuroblastoma Amplified Sequence Gene) known to be associated with acute liver failure are also responsible for skeletal abnormalities. This work was published as a novel cause of bone fragility [Balasubramanian *et al*., 2017]. NBAS role in bone fragility provides an opportunity to use tractable animal research to advance understanding of mechanism and identify potential new treatments. This would be beneficial to patients but also inform on a wider front regarding cell membrane trafficking and effect on collagen secretion.

Objectives

Hypotheses:

- NBAS is required for cargo-selective, tissue-specific secretion/ glycosylation of collagen within cell;
- Identifying druggable targets to rescue NBAS activity will reverse disease phenotype.

Methods

1. In-depth analyses of skeletal manifestations and phenotype of homozygous mutant fish we have generated for a nonsense nbas allele.
2. Screening assays to rescue Nbas activity in mutant fish model to identify candidate small molecules.

Results

We decided to analyse an nbas mutant fish line, the predicted null mutation (sa16290) from EZRC stock center which have been grown up to adult fish. We have raised three generations of homozygous mutant fish to generate a mutant line that has a specific defect with Mendelian ratios, without any background mutations. The nbas mutant fish can be identified at between 4 and 5 days post fertilization (dpf), as they fail to inflate their swim bladder. We have analysed

nbas mutants for skeletal manifestations and cartilage staining has revealed disorganised and rounded chondrocytes in the jaw. In comparison, wild-type embryos have chondrocytes that are uniform in size and stacked to form an organised structure. Day 5 Alcian Blue stain revealed chondrocytes neatly stacked in wildtype fish and more disorganised and rounded in homozygous nbas mutant fish. We are currently undertaking further studies to analyse in-depth nbas mutant fish and preliminary drug screening which will be presented.

Conclusion

Patients with NBAS mutations are subjected to lifetime of recurrent fractures, repeated episodes of acute liver failure needing recurrent hospital admissions and immune deficiency. Developing druggable targets towards making this condition better would have a positive impact on quality of life for patients.

Disclosure

The authors declared no competing interests.

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OC21

New mouse model with IFITM5 S42L for atypical type VI osteogenesis imperfecta

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Objectives

Osteogenesis Imperfecta (OI) is a collagen-related disorder. Type V OI, caused by a recurrent dominant mutation in the plasma membrane protein IFITM5/BRIL, and type VI OI, caused by recessive null mutations in the anti-angiogenic factor PEDF, have distinct features. IFITM5 S40L, reported in six patients, causes severe dominant OI with phenotype and bone histology similar to type VI, rather than Type V, OI. Our objective is to understand the pathway connecting IFITM5 and PEDF and its role in bone development.

Methods

We generated a conditional knock-in mouse model to investigate atypical type VI OI. The mutation, located at murine BRIL S42L, was activated using E2A-CRE mating. Heterozygous and homozygous mutant mice were analyzed at 1 and 2 months of age.

Results

BRIL S42L is non-lethal in both heterozygous and homozygous mice. Newborn heterozygous and homozygous S42L pups have flared rib cage, shoulder and knee dislocations, plus homozygotes have rib fractures and unmineralized calvaria. In radiographs, S42L heterozygous mice exhibit ⏲60% humeral fractures in 1- (19/30 HETS) and 2-month-old (18/28 HETS) mice, while homozygotes incur fractures in 96% (30/31 HOMZ) of humerii, as well as femora and pelvis. Serum alkaline phosphatase was increased in 1-month-old heterozygous males ($P<0.01$) wrt WT, as occurs in typical and atypical OI type VI. Femora of 2-month old heterozygous males showed elevated TbN ($P<0.05$) on uCT, reduced stiffness, yield and ultimate load, with marked increase in brittleness. Biomechanics are not explained by change in bone size, suggesting material differences. Pore volume/BV was increased on uCT, consistent with increased vascularity. Whole body DXA aBMD was significantly decreased in 1 and 2 month-old heterozygotes ($P<0.01$) and 1-month-old S42L homozygotes. qBEI revealed increased mineralization in cancellous and cortical bone of 2 month-old heterozygous males. This is consistent with *in vitro* osteoblast studies from heterozygous mice which yielded increased mineralization by alizarin red staining ($P<0.05$) and increased expression levels of osteoblast genes throughout differentiation.

Conclusion

Taken together, the altered bone fragility, mineralization, vascularity and serum ALP indicate that the IFITM5 S42L mouse is an appropriate model to investigate the cellular and bone tissue mechanisms of atypical type VI OI.

Disclosure

The authors declared no competing interests.

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OC22

Bone tissue phenotyping reveals increased matrix mineralization, elevated osteocyte lacunar density and altered vascularity in a new OI mouse model carrying a leucine substitution for the BRIL p.Serine42 residue

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Objectives

A common feature of nearly all forms of osteogenesis imperfecta (OI) is a hypermineralized bone matrix. Null mutations in SERPINF1, encoding the potent antiangiogenic factor PEDF, lead to type VI OI with excessive osteoid formation, abnormal osteoblast-osteocyte development and increased matrix mineralization. Recently, atypical type VI OI has been delineated, caused by a loss-of-function mutation (p.S40L) in IFITM5 the causative gene for type V OI. The 6 cases reported to date have very severe OI, normal PEDF serum levels, but, similar to OI type VI, reduced PEDF secretion by osteoblasts. To gain further insights into the bone material properties, vascularization and thus pathophysiology of atypical type VI OI, we investigated a new knock-in (KI) mouse model carrying a leucine substitution for the BRIL p.Serine42 residue.

Methods

We analyzed longitudinal sections of distal femurs of 8 weeks-old heterozygous male mutants (KI, $n=10$) and wild-types (WT, $n=9$) using quantitative backscattered electron imaging (qBEI). Bone mineralization density distribution (BMDD) was measured in cancellous metaphyseal- and midshaft cortical bone. Osteocyte lacunae sections (OLS) were characterized in cortical bone. Structural histomorphometric parameters were evaluated in cancellous bone. We used X-ray microcomputed tomography (micro-CT) to evaluate vascularization in the femoral third trochanter.

Results

qBEI revealed that bone matrix mineralization was markedly increased in KI compared to WT cancellous (CaPeak: $+2.38\%$, $P=0.0331$) and cortical bone (CaPeak: $+2.81\%$, $P=0.0085$; CaMean: $+2.48\%$, $P=0.0023$; CaWidth: $+11.24\%$, $P<0.0001$, CaHigh: $+51\%$, $P=0.0027$). We further observed in KI mice an increased OLS density ($+23.11\%$, $P<0.0001$) and decreased OLS mean area and perimeter (-20.25%, $P<0.0001$; -13%, $P<0.0001$, respectively) versus WT. Histomorphometry revealed no changes of mineralized BV/TV, BS/TV, Tb.N and Tb.Th between the two genotypes. Micro-CT analyzes yielded increased pore volume/bone volume in KI ($+14.28\%$, $P=0.044$) mirroring increased vascularity.

Conclusion

Our new mouse model for atypical type VI OI has elevated bone matrix mineralization and altered osteocyte lacunae characteristics similar to those of type VI OI. The increased bone vascular volume is consistent with defective PEDF secretion in bone as reported in affected patients. Further analysis of osteoblasts function and osteoid formation will provide additional insights in atypical OI type VI.

Disclosure

The authors declared no competing interests.

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OC23

Effects of the FGF2 aptamer on growth plate cartilage development of achondroplasia patient-specific iPS cells in a xenograft model

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Objectives

Endochondral ossification in the growth plate cartilage (GPC) plays a crucial role in the determination of the length and shape of long bones. Many skeletal dysplasias are caused by GPC dysfunction, associated with short stature. We have already reported that human iPS cell-derived cartilage (hiPSC-Cart), when implanted into the subcutaneous spaces of the SCID mice for 4 weeks, formed skeletal tissue like GPC. This model could also recapitulate the pathology of FGFR3-related skeletal dysplasia (Osteoarthritis and Cartilage 2018). In the study, we applied our hiPSC-GPC model to the evaluation of candidate drug efficacy for FGFR3-relaed skeletal dysplasia.

Methods
We used 3 hiPSC lines derived from patients with achondroplasia (ACH) and one healthy control. A RNA aptamer, RBM-007, specific for human FGF2 and confirmed the blocking effect in signaling pathway induced by FGF2 *in vitro* was used as a candidate drug for ACH. First, ACH-hiPSCs were chondrogenically differentiated with various concentration of RBM-007. Then, ACH-hiPSC-derived cartilages were transplanted into SCID mice (a xenograft model). Four mice were treated with RBM-007, and the other 4 mice were treated with vehicle. Grafts were removed 6 weeks after transplantation and subjected to histological analysis.
Results
In *in vitro* experiments, control hiPSCs differentiated into chondrocytes and produced cartilage matrix, while ACH-hiPSCs did not differentiate into chondrocytes. 100 nM, but not 10 nM, RBM-007 promoted the chondrogenic differentiation of ACH-hiPSCs with characteristic safranin-O-positive matrix formation and improved the expression of the chondrocyte marker genes such as COL2A1. As a result of the xenograft model, histological analysis showed that control hiPSC-GPC had a zonal arrangement similar to GPC and is associated with bone formation. Each zone expressed marker gene such as type X collagen. Hypertrophic cells in ACH-hiPSC were smaller than those in control hiPSC-GPC. Treatment with RBM-007 improved the pathology of ACH, but did not normalize the hypertrophic cell size.
Conclusions
The experiments of the xenograft model suggest that RBM-007 is a potential drug for achondroplasia.
Disclosure
Keiichi Ozono is an adviser of Ribomic Inc. and had honorarium from Ribomic Inc. Yosuke Nonaka, Masatoshi Fujiwara, Yoshikazu Nakamura are employees of Ribomic Inc.

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OC24

TA-46, a recombinant soluble FGFR3 receptor for the treatment of achondroplasia, is safe and well-tolerated in healthy volunteers

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Objectives
To assess the safety, tolerability and pharmacokinetic (PK) profile of single and multiple doses of TA-46 administered subcutaneously to healthy volunteers.
Methods
This was a double-blind, randomized, placebo-controlled trial in a total of 72 subjects. Cohorts of 8 subjects were randomised to receive either TA-46 or placebo in a 3:1 ratio in single ascending dose (SAD) and multiple ascending dose (MAD) cohorts. SAD doses were 0.3, 1, 3, 10 and 20 mg/kg. MAD cohorts received 4 weeks of treatment either twice weekly (1 mg/kg, 3 mg/kg) or once weekly (3 mg/kg, 10 mg/kg) subcutaneously (s.c.). The study was approved by the local research ethics committee.
Results
All doses of TA-46 were safe and well tolerated. No serious adverse events (SAEs) were reported. TA-46 related AEs were injection site reactions (ISRs), of which over 90% were mild. PK analysis showed Cmax at 48–96 h and t1/2 of 48–93 h. The PK of TA-46 after single and multiple s.c. administrations is approximately dose proportional in the range 0.3–3 mg/kg and can be described by a one-compartment PK model.
Conclusions
Single and multiple s.c. doses of TA-46 were safe and well tolerated. Mild ISRs were seen in once weekly dosing which, alongside the PK analysis, supports a once weekly dosing regimen of TA-46 in achondroplasia.
Disclosure
All authors are employees of Therachon AG.

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OC25

TransCon CNP: Potential for a once weekly novel therapy in children with achondroplasia

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Objectives
Achondroplasia (ACH), the most common form of human dwarfism, is caused by a gain-of-function mutation in the fibroblast growth factor receptor 3 (FGFR3) gene, a key negative regulator of endochondral ossification. C-type natriuretic peptide (CNP) inhibits the FGFR3 pathway and thereby promotes proliferation and differentiation of chondrocytes to promote bone growth. TransCon CNP is a prodrug designed to provide continuous exposure to CNP to optimize efficacy with a well-tolerated and convenient once-weekly dose. The objective of the TransCon CNP phase 1 trial was to evaluate the safety, tolerability, and pharmacokinetics of subcutaneous single ascending doses of TransCon CNP.
Methods
To initiate the clinical development of TransCon CNP, a phase 1 trial in healthy adult male subjects was completed; 45 subjects participated in a double-blind, placebo-controlled, dose escalation trial.
Results
The trial confirmed that one dose of TransCon CNP (administered at 3–150 μg CNP/kg) provided continuous systemic exposure over 7 days to active free CNP released from the prodrug by a predictable non-enzymatic process depending on physiologic temperature and pH. A dose-related increase in CNP exposure was observed with a mean Cmax obtained with a single dose of 10 μg CNP/kg of 2.6 picomolar (pM) that increased to 42 pM with a single dose of 150 μg CNP/kg. Maximum plasma concentrations were reached 2–3 days post-dose and, after 7 days post-dose, the levels were reduced by approximately 2-fold. Plasma concentration of free CNP is dictated by the kinetics of the prodrug and the long linker release half-life, resulting in an effective half-life of CNP of ~90 hours (in contrast, native CNP has a half-life of ~2 minutes), which supports a once-weekly dosing regimen. No serious adverse events were reported and TransCon CNP was generally well-tolerated. Mean resting blood pressure and heart rate were unchanged from pre-dose baseline. In addition, mean orthostatic changes in vital signs were consistent between placebo and TransCon CNP cohorts.
Conclusion
This phase 1 TransCon CNP trial in heathy subjects suggests the potential of a safe and efficacious once-weekly therapy in children with achondroplasia. Further studies should be evaluated to confirm and extend these findings.
Disclosure
All authors are employees of Ascendis Pharma.

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OC26

[18F] NaF PET/CT the first tool to diagnose chronic activity in FOP at all ages?

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Fibrodysplasia ossificans progressiva (FOP) is a rare, autosomal dominant disorder characterized by heterotopic ossification (HO) in muscles, ligaments and tendons. Flare-ups often precede formation of HO, resulting in immobilized joints. Recently, it has been shown that [18F]NaF PET/CT could identify early ossifying disease activity during flare-ups. HO may progress without signs of flare-up, but its underlying physiology is not understood. We wondered whether [18F]NaF PET/CT could identify this silent progression of FOP. Therefore we analysed [18F]NaF PET/CT follow-up data in a small group of FOP patients during several years and investigated which HO progressed in the absence of flare-up. Intriguingly, we found in 4 out of 5 patients one or more progressive HO lesions related to activity on the [18F]NaF PET/CT scan. Hereby we demonstrated the co-existence of chronic activity of FOP leading to silent progression of HO. In fact in all four late adolescent and young adults we found chronic progression of disease activity without clinical symptoms. The duration of this chronic FOP phase is unknown. But previously we observed in a young patient chronic continuous activity of HO on bone scintigraphy with increasing contracture during her growth over >10 years. This may indicate that HO can be chronic active for a long time. Future drugs should target not only HO formation after flare-ups, but should also stop progression in this chronic phase. In rare bone disease well measurable endpoints are scarce. However inhibition of quantifiable activity in FOP as assessed by [18F]NaF PET/CT scanning could be used as a hard endpoint in drug studies. At this moment this imaging modality is used in one trial (Lumina-1, Regeneron Pharmaceuticals) and will also be used in a new upcoming European trial. During the first decade of life, most children with FOP already develop moderate to severe disabling HO. It is therefore important to study the role of the chronic activity in young people which might be longer after a flare up. At this moment we are developing careful procedures of [18F] NaF PET/CT scanning in young children to study the course of the disease and to develop drug strategies.

Disclosure
Cooperation in clinical trial Lumina-1 of Regeneron Pharmaceuticals.
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OC27

Palovarotene inhibits the development of new heterotopic ossification in fibrodysplasia ossificans progressiva (FOP)

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Objective
FOP is a rare, severely disabling disease characterized by episodic flare-ups and accumulation of heterotopic ossification (HO) leading to restricted movement, physical disability, and early death. Data from two Phase 2 interventional studies and one natural history study (NHS) were used to evaluate whether palovarotene could reduce HO following an FOP flare-up.
Methods
HO volume at the flare-up site was determined by CT at baseline and 12 weeks post-baseline; baseline edema was determined by MRI/US. Palovarotene regimens included: flare-up only 10/5 mg for 2/4 weeks (48 flare-ups/27 subjects; mean/median age (range) = 23/22 years (9–44); 52%male); flare-up only 20/10 mg for 4/8+ weeks (18 flare ups/12 subjects; 14/11 years (7–34); 33%male); 5 mg daily (chronic) plus 20/10 regimen during flare-up (33 flare-ups/23 subjects; 25/25 years (13 46); 35%male). The comparator pooled data from a randomized placebo group and untreated NHS flare-ups (49 flare-ups/41 subjects; 17/14 years (4 53); 49%male). Flare-ups most commonly occurred in the hip, knee, lower back, and shoulder in all groups. All imaging was interpreted by a blinded, central laboratory using pre-specified procedures.
Results
The difference in new HO volume between the 20/10 flare-up regimen (3,045 mm^3) and placebo/untreated flare-ups (11,014 mm^3) was statistically significant (95% CI = 27,379 mm^3, 2,253 mm^3; $P = 0.02$; ANOVA with BCa bootstrap and covariate adjustment), representing a 72% reduction in new HO volume. Reductions versus controls were similar with the chronic/flare-up (3,018 mm^3; $P = 0.16$) and 10/5 flare-up regimens (2,731 mm^3; $P = 0.05$). The proportion of flare-ups with baseline edema that formed new HO was 40% in the placebo/untreated group, 60% in the 10/5 group, 50% in the 20/10 group, and 27% in the chronic/flare-up group. Dose-related increases in adverse events, mainly mucocutaneous in nature, were observed. There were no apparent effects on ECG findings or on growth in skeletally immature subjects.
Conclusions
Data from 148 prospectively assessed flare-ups demonstrated an ~70% decrease in new HO volume at week 12 following palovarotene administration when compared to the placebo/untreated control. The impact of the chronic/flare-up regimen on whole body HO volume is being evaluated in a Phase 3 trial. Palovarotene was tolerated at the doses administered. We thank the FOP community and clinical research teams
Disclosure
Donna Grogan is an employee of Clementia Pharmaceuticals Inc.
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Poster Presentations

P1

Abstract withdrawn.

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P2

Treatment of partial growth arrest using cylindrical costal osteochondral graft

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Objective
Growth plate injury can lead the development of angular deformities and limb length discrepancies in growing children. Current several treatments can't regenerate the damaged cartilage adequately. In this study, we investigated the feasibility of the transplantation of cylindrical costal osteochondral graft to establish a new regenerative treatment for growth arrest.
Methods
An experimental model of partial growth plate injury was created by resecting the medial part of the proximal tibial growth plate in male six-week-old New Zealand White rabbits. The rabbits were divided into three groups: control (no transplantation), bone wax transplantation (current treatment), costal osteochondral graft. The angular deformities of the tibia and bony bridge were analyzed using radiographs and μCT, and the repair of the injured growth plate cartilage and bony bridge formation were histologically evaluated at four and eight weeks post-operatively.
Results
The mean MTPA was 69.9°(59.0° to 84.0°) at four weeks, and 50.3°(37.0° to 65.9°) at eight weeks post-operatively in the control group, 79.8°(70.0° to 90.0°) at four weeks, and 62.0°(56.0° to 69.0°) at eight weeks post-operatively in the bone wax group, 81.7°(74.0° to 92.7°) at four weeks and 68.8°(64.2° to 74.3°) at eight weeks post-operatively in the osteochondral graft group. In the control group, bony bridge replaced injured growth plate. In the bone wax group, some cases showed disappearance of transplanted bone wax and replacement with a bony bridge and few chondrocyte-like cells were seen at eight weeks post-operatively. In the osteochondral graft group, the growth plate were thickened, continuous and proliferative and prehypertrophic chondrocytes-like cells were newly formed at the site of growth plate injury and the cells took on a columnar arrangement like normal physis at eight weeks post-operatively.
Conclusion
Cylindorical costal cartilage graft transplantation can prevent the formation of a bone bridge and promote the regeneration of injured growth plate.
Disclosure
The authors declared no competing interests.

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P3

Abstract withdrawn.

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P4

Applicability of the Tanner-Whitehouse 3 method to United Kingdom children born in the 21st century

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Background
To assess the effect of secular change on skeletal maturation and thus on the applicability Tanner and Whitehouse (TW3) methods of bone age estimation.
Methods
A single observer assessed bone age using BoneXpert software on 392 hand/wrist trauma radiographs (206 males, 257 left, age range 2 to 15 years, 296 Caucasians, 71 Asians, 20 Africans, 5 mixed Caucasian and Asian) performed in the period 2010–2016. The paired sample t test was used to indicate the difference between mean bone age (BA) and mean chronological age (CA). ANOVA was used to assess the differences between groups based on socioeconomic status (taken from the index of multiple deprivation). The standard error of the estimate (SEE, in ± years) for both sexes was calculated.
Results
Chronological age ranged from 2 to 15 years for females and 2.5 to 15 years for males. Numbers of children living in low, average and high socioeconomic areas were 216 (55%), 74 (19%) and 102 (26%) respectively. The TW3 BA was underestimated in females compared to chronological age beyond the age of 3 years, with significant differences between BA and CA (−0.43 years ±1.05 $P = <0.001$) but not in males (0.01 years SD 0.97, $P = 0.76$). Of the difference in females, 17.8% was accounted for by socioeconomic status. Despite the statistically significant observed difference between BA and CA, the TW3 showed comparable accuracy in females and males with SEE of ±1.06 and ± 1.00 years, respectively.
Conclusion
Secular change has not advanced skeletal maturity of present-day UK children compared to those of the mid-20th century.
Disclosure
The authors declared no competing interests.

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P5

Response of bone to mechanical stimulation in the offspring of MAVIDOS study mothers in a single centre; the effect of antenatal vitamin D supplementation

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Background
Preclinical model studies suggest early life vitamin D depletion reduces bone's response to mechanical loading. The MAVIDOS trial (randomised placebo controlled trial of vitamin D supplementation in pregnancy) reported winter-born infants of mothers receiving vitamin D supplementation had higher bone mass; the earlier Southampton Princess Ann Cohort study linked pregnancy blood vitamin D levels to later bone mass and size. We showed previously that bone responds quickly to short periods of mechanical stimulation. This study aimed to determine whether antenatal vitamin D supplementation alters postnatal bone formation in response to mechanical stimulation.
Methods
Thirty-one children (4–5 years age) born to mothers who participated in MAVIDOS during pregnancy and received placebo [$n = 19$] or Cholecalciferol 1000IU/day [$n = 12$] were recruited. Children received whole body vibration (WBV; LivMd vibrating platform) for 10 minutes (4×2.5 minutes interspersed with 30 seconds rest) on 5 consecutive days. Fasting blood samples for bone homeostasis, including 25-hydroxyvitamin D (25OHD) and parathormone (PTH), and turnover markers (P1NP, CTX) were collected pre-WBV and on D8.
Results
Bone profile including serum 25OHD and PTH were normal in the entire cohort; there were no significant differences between groups. Median (25th/75th centiles) P1NP (ng/mL) at baseline within placebo and vitamin D-supplementation groups were 587.1(518.2,801.7) and 552.2(512.3,678.6). Mean changes (Δ) in P1NP (ng/ml) between baseline and D8 in the supplementation and placebo groups respectively were 40.6 and −92.6; between group difference in ΔP1NP 133.2 ng/mL [95% CI 0.4,266.0; $P = 0.049$]. Median (25th/75th centiles) for CTX (ng/mL) at baseline within the placebo and supplementation groups were 1.59(1.3,1.81) and 1.52(1.29,1.81) respectively. The mean changes in CTX (ng/ml) between baseline and D8 in the supplementation and placebo groups respectively were −0.034 and −0.084 ng/ml; between group difference in ΔCTX 0.05 ng/ml (95% CI = −0.159,0.26 ng/mL; $P = 0.62$).
Conclusion
Following vitamin D supplementation in pregnancy, P1NP increased significantly more in response to WBV compared to children whose mothers had received placebo. This implies early life vitamin D supplementation increases the anabolic

response of bone to mechanical loading in children; given the limited sample size, confirmation in a larger cohort is needed, along with prospective data collection on fractures.
Disclosure
NJB consults for Alexion, Mereo, UCB and Amgen, and receives grant support for clinical studies from Alexion and Amgen.
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P6

Pseudohypoparathyroidism type Ib initially masquerading as epileptic seizures due to Fahr's disease

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Background
Hypocalcaemia can be manifested by paresthesia, muscle cramps, muscle weakness, syncope, convulsions and even severe psychomotor retardation. Suchs symptoms can be initially considered as signs of epilepsy. Fahr's disease is neurological disorder with neuropsychic changes and convulsions. Fahr's disease is characterized by central nervous system calcifications caused by mutations in SLC20A2 gene, encoding sodium-dependent phosphate transporter 2 (PiT-2) that plays a major role in phosphate homeostasis by transporting phosphate across cell membranes. Once the calcifications are secondary to a known cause, the disease is referred to as Fahr's syndrome.
Case Report and Clinical Management
We present a12-year old patient with partial seizures, myalgias, psychomotor retardation, and basal ganglia calcifications, initially diagnosed as having Fahr's disease and epilepsy, where severe chronic hypocalcaemia, due to genetically confirmed pseudohypoparathyroidism type Ib (PHP Ib) was the real underlying cause. Genetic examination did not conmfirm Fahr's disease as mutations in the SLC20A2 gene were NOT found. Mutational analysis of GNAS gene by Multiple-Ligation Probe amplification (MLPA) confirmed the diagnosis of pseudohypoparathyroidism type Ib (PHP Ib), due to methylation changes of exon I and GNAS promotor on 20q13.32. Therefore, the final diagnosis was PHP Ib with Fahr's syndrome. Excellent clinical improvement was observed after calcium and vitamin D therapy. Currently, the boy is 16 years old, on daily calcium (1500 mg/day) and vitamin D supplementation (cholecalciferol 10 000 IU/day) and calcitriol (0.5 µg/day). His S-Ca, S-P and S-PTH are within reference ranges, he is free of convulsions, mentally fit and physically very active, without any cramps or myalgias.
Discussion and Conclusion
The serum evaluation of minerals, especially calcium and phosphate, should be performed in all patients with convulsions, cramps and psychomotor retardation. This is essential in arriving at a proper diagnosis and early initiation of appropriate treatment.
Disclosure
The authors declared no competing interests.
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P7

Bone morphology patterns in children with osteogenesis imperfecta

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Objectives
The objective of this study is to characterize patterns of bone morphology in children with osteogenesis imperfecta (OI), using measurements of the second metacarpal. A secondary objective is to look for impact of bisphosphonate treatment on bone morphology in this population.
Methods
This is an IRB-approved retrospective review of 82 de-identified bone age films (AP hand/wrist) for 42 children with OI (17M, 25F). Measurements (Sectra IDS 7 PACS) included metacarpal length, width, and cortical thickness. Robustness (total area/length) and relative cortical area (RCA, cortical area/total area) were calculated to analyze metacarpal size and strength. Charts were reviewed to determine if they received bisphosphonate treatment within two years prior to the hand x-ray. Measurements were compared to 54 hand radiographs from 28 healthy controls (14M, 14F). Control ages ranged from 3 to 14. Non-parametric Kruskal-Wallis tests were used to compare differences in bone characteristics between study groups ($P < 0.05$).
Results
Twenty-six untreated people with OI (7M, 19F) were included and typed as follows: type 1: 13; type 3: 4; type 4: 6; type V: 1; type 8: 1; type 9: 1. Ages ranged from 5 months to 14 years. 16 individuals treated with bisphosphonates (10M, 6F) were included and typed as follows: type 1: 3; type 3: 6; type 4: 4; type 5: 1; type 9: 1; unknown recessive: 1. Ages ranged from 2 to 14 years. All individuals with OI displayed decreased robustness, metacarpal width and length, and cortical thickness compared to the control group ($P < .0.001$). There were no significant differences between treated and untreated OI groups. Control males displayed higher robustness, width, length, and cortical thickness to females ($P < .0.001$). No sexual dimorphism was observed within OI groups.
Conclusion
People with OI had decreased robustness compared to controls, suggesting that OI bones are slender. Slender bones are structurally weaker compared to wider, more robust bones. Decreased cortical thickness has been found to correlate with decreased bone strength. These factors contribute to bone fragility of the OI population. Biological differences in the control populations are sex-specific, while no sexual dimorphism was noted for individuals with OI. Therefore, OI genotype trumps sex.
Disclosure
OI Foundation - Grants/Research Support, Advisory Board or Panel. EDS - Advisory Board or Panel. Biomarin - Consultant, Speaker's Bureau, Advisory Board or Panel. Alexion - Speaker's Bureau. Ascendis - Advisory Board or Panel.
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P8

Polyhydramnios: sole risk factor for non-traumatic fractures in two infants

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Bone loading is a primary determinant of bone strength in later childhood and adulthood. Our understanding of how mechanical stimuli generated by foetal kicking and movements impact skeletal development is still limited. Many studies suggest that a sufficient and balanced supply of energy, proteins, vitamins, calcium, phosphorus, and other nutrients is an essential prerequisite for normal bone development. However, only few studies highlight the contribution of the biomechanical environment in utero on the fetal skeleton. Recent studies have provided new insight suggesting a role for stress stimulation in ossification events and for strain stimuli in joint morphogenesis. This stimulation is known to be critical for prenatal musculoskeletal development. Infants whose movement in utero is reduced subsequently suffer from joint dysplasia and thin hypomineralized bones and demonstrate that embryonic movement is crucial for appropriate skeletogenesis. This has been confirmed in different animal models. We present the cases of two patients seen in our Bone Clinic at Sainte-Justine University Hospital between 2013 and 2018. They all presented fractures of lower limbs at an early age (2,5 and 5 months respectively), and were found to have low bone mineral density upon DXA testing. A shared characteristic between patients was that all two pregnancies presented with a polyhydramnios of unknown etiology in the third trimester, as assessed by routine ultrasound. They presented no family history of bone disease, and genetic testing for neuromuscular diseases or bone fragility was negative in all patients. They showed to be catching up on bone mineral density within the year following the onset of fractures without receiving anti-osteoporotic treatments. Based on the mechanostat theory, we hypothesize that polyhydramnios plays as a significant risk factor for low bone mineral density. A larger amount of liquid in the amniotic cavity could limit the rate and intensity of limb loading, resulting in lower peak force applied on the spine as well. To the best of our knowledge, this is the first case series to investigate a connection between polyhydramnios and bone strength in the perinatal period. It could lead the way to researches connecting pre-birth biomechanical factors to bone health in infancy.
Disclosure
The authors declared no competing interests.
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P9

Do lifestyle factors play a role on bone health in boys diagnosed with Autism Spectrum Disorder? Preliminary data from the Promoting bone and gut health in our children (PROUD) study

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Objective
Autism Spectrum Disorder (ASD) is associated with lower bone mass in children. Physical activity and nutrition influence bone pathophysiology, and differences in these lifestyle factors are observed between children with vs. without ASD; however, whether these factors contribute to bone differences is unknown. We examined if: 1) differences existed in bone mineral density (BMD), content (BMC), or bone geometry in boys with vs without ASD and 2) whether physical activity and/or total energy-intake influenced those differences.
Methods
Preliminary case-control data included 44 boys (22 with (cases) and 22 without (controls) ASD), matched for age (12.3($\pm$1.8) yrs) and height (155($\pm$11) cm). Lumbar spine, total hip, femoral-neck (FN) and total-body-less-head BMD and BMC were assessed with dual energy X-ray absorptiometry. Hip structural analyses estimated bone geometry (cross-sectional area (CSA), minimal-neck-width and section modulus (Z)) (Encore v16.2). Moderate-to-vigorous physical activity (MVPA) was measured using Actigraph accelerometers, and total energy-intake was assessed using a 3-day food diary. BMD, BMC, and bone geometry were compared between groups, and multivariable regression models were used to investigate whether MVPA and/or total energy-intake influenced bone differences between cases and controls.
Results
In weight-adjusted models, cases had 8–13% lower BMD at all sites than controls (all $P<0.05$): in fully adjusted models, neither total energy-intake nor MVPA explained these differences. After adjusting for weight, cases vs controls had 11% lower BMC; however, in contrast to BMD, this was only observed at the FN. After BMC models were further adjusted for lifestyle factors, associations at the FN were sustained (β -0.262, S.E. ± 0.107, $P=0.02$): energy-intake was significantly associated in this model, but not MVPA. For bone geometry, and independent of weight, cases vs controls had 11% lower CSA ($P=0.01$). In fully adjusted models, energy-intake contributed to lower CSA (β -12.269, S.E. $\pm$ 4.931, $P=0.02$) in cases; however, Z did not differ ($P=0.30$), suggesting a preservation of strength in bending.
Conclusion
Boys with ASD had lower BMD and BMC that were not explained by differences in total energy-intake or MVPA. Further work should examine whether and to what degree specific patterns of dietary intake and physical activity contribute to underlying pathophysiological differences in bone.
Disclosure
The authors declared no competing interests.

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P10

Radiographic evidence of zoledronic acid given during pregnancy – a case report

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Background
A 3.2 year old boy was reviewed following 2 low trauma femoral fractures. He had been born at 31 weeks gestation, his mother having been diagnosed with metastatic breast cancer at 12 weeks gestation. She received chemotherapy at 20 weeks gestation and was given intravenous zoledronic acid (ZA) during the second trimester for hypercalcaemia.
Presenting problem
At 2.7 years, he fell on a tarmacked surface sustaining a diaphyseal fracture of his right femur which was managed with a hip spica. At 3.2 years, he sustained a fracture of his left femur when he fell from standing onto a cushion. Bone biochemistry was normal (apart from a 25OH vitamin D 48 nmol/L - subsequently treated).
Clinical Management
Examination revealed blue sclerae and hypermobile joints. Dentition was normal. There was no family history of bone disease. A clinical diagnosis of type 1 osteogenesis imperfecta was made. DXA was unremarkable (L2-4 BMD 0.588 g/cm^2; Z score -0.4). A lateral spine radiograph was undertaken to exclude vertebral loss of height/fractures. Whilst no fractures were found there was a strikingly unusual radiographic appearance; there was a well-defined rectangular area of hyperdensity in the centre of each vertebra, with lower density bone around it. The appearance was suggestive of a retained calcified scaffold of each vertebra from an earlier point in growth. The view of the clinicians and radiologist was that the cause of this 'bone-in-bone' appearance was consistent with and likely to be due to the ZA administered to the child's mother during the second trimester of pregnancy. Joint review with a clinical geneticist resulted in agreement that the clinical diagnosis was sufficiently clear to render COL1A1/COL1A2 screening unnecessary.
Discussion
Adverse effects of bisphosphonates on the fetal skeleton have been observed in animal studies, although often with doses much higher than those used in clinical practice. However no long-term health consequences have been reported in any infant. In this case study we report persisting skeletal abnormalities in the fetus caused by exposure to bisphosphonates during pregnancy. Further studies are needed to confirm the safety of bisphosphonate use during pregnancy on the fetus and the neonate.
Disclosure
Nick Bishop: Consults for Alexion, Mereo, UCB and Amgen, and receives grant support for clinical studies from Alexion and Amgen. Paul Arundel: Research grant/honoraria/ expenses - Alexion and Kyowa Kirin. Expenses - BioMarin Amaka C. Offiah: Research grant/honoraria/ expenses – Alexion. Honoraria/ Expenses - BioMarin

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P11

Reference values of cortical thickness, bone width, and Bone Health Index in metacarpals of children from age 0 y, as determined with an extension of the fully automated BoneXpert bone age method

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Objective
The BoneXpert method for automated bone age determination from hand X-rays also determines the cortical thickness T and the bone width W in the three middle metacarpals. From these, the method derives the cortical area $A=\pi$ W T (1 – T/W), the metacarpal index MCI $=A/(WW)$ and the Bone Health Index. Recently, the method has been extended down to new-borns, and the aim of this study is to report reference curves for these bone measures.
Method
410 healthy children born in Paris in 1955 were followed with hand X-rays at ages 1, 3, 6, 9, 12 and 18 months, and then annually until age 20 years. Reference curves were defined versus bone age (BA) determined automatically on the Greulich Pyle scale, averaging over radius, ulna and 19 short bones.
Results
For males, the cortical thickness drops from 0.74 mm at BA 0.08 y to a minimum of 0.58 mm at BA 1.0, a reduction by 22%. Bone width increases by 38% from 3.2 to 4.4 mm in the same period, and cortical area grows by 19%. Bone length increases 43% from 16.6 to 24 mm. MCI drops from 0.55 to 0.37 (33%) and BHI from 4.8 to 3.4 (29%) in the same period. Females display a similar development, but their cortical thickness assumes its minimum at BA 0.9 y.
Conclusion
Infants exhibit a dramatic reconfiguration or bone geometry in the first year of life with strongly increasing width and length, and cortical thickness decreasing by 22%. MCI and BHI decrease in this period – could it explain the increased fracture risk in children at age 1.0 compared to new-borns? (Hedström *et al*., Epidemiology of fractures in children and adolescents. Acta Orthop. 2010) – surely, more studies are needed to assess the relationship between bone indices and fracture risk. The method could be more useful clinically than DEXA in infants, because (1) it is easier to record a hand X-ray, (2) the new reference curves provide Z-scores relative to the normal French population, and (3) the reference curves are expressed versus bone age rather than age.
Disclosure
HHT is owner and PT is employee of Visiana who develops the BoneXpert method for automated bone age and Bone Health Index determination.

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P12

Abstract withdrawn.

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P13

Clinical implications of modeling the maturational spurt

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Objective
The treatment of many skeletal growth and/or developmental disorders often relies on a child's biological maturity status, frequently determined by a skeletal maturity assessment. Rapid changes in the rate of skeletal maturation (i.e., the maturational spurt) during adolescence can significantly influence biological maturity status, affecting treatment type and timing as well as clinical outcomes. However, the chronological age at which peak maturational velocity (aPMV) is achieved is dependent on maturational trajectory form (i.e., curve form) – a characteristic that is difficult to predict. We aimed to determine how trajectory form influences aPMV for future application in pediatric clinical practice.
Methods
We used skeletal maturity assessments (Fels Method) of serial left hand-wrist radiographs from 214 participants (126 boys; 88 girls; 6,659 total observations) between the chronological ages of 3 and 20 years from the Fels Longitudinal Study. Maturational trajectories were modeled for each participant using both 4th and 5th order fixed effect polynomials; Akaike's Information Criterion for Finite Sample Sizes (AICc) was used to determine the best model. Estimates of aPMV were calculated for each participant and compared between models (i.e., best fit vs. other) using a two-sided t-test with statistical significance set at ≤ 0.05.
Results
Estimates of aPMV from both 4th and 5th order fixed effect polynomials were not significantly different in either boys or girls. Nevertheless, aPMV was consistently earlier (boys, 8 months; girls, 1 month) in participants best fit with 5th order polynomials when modeled by 4th order polynomials. Similarly, aPMV was slightly later (boys, 2 months; girls, 1 month) in participants best fit with 4th order polynomials when modeled by 5th order polynomials.
Conclusion
In the present study, modeling maturational trajectories with 5th order polynomials appeared to have later estimates of aPMV, particularly in boys, than those derived from 4th order polynomials, despite non-significance. Because clinical treatment and outcomes could be negatively impacted by underestimating developmental milestones, such as aPMV, we advocate the use of 5th order polynomials to estimate aPMV.
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Disclosure
The authors declared no competing interests.

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P14

Bone health in children with congenital heart disease

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Objectives
Children with congenital heart disease (CHD) have been found to have markedly low levels of physical activity (PA) compared to typically developing peers. It is well known that PA during the growing years has a beneficial effect on bone health with the most active children laying down more bone than their less active peers. If children with CHD are avoiding PA, current and future bone health may be compromised; however, very little is known of the bone health of children with CHD. The purpose of this study was to investigate the bone density and estimated strength of children with CHD.
Methods
Thirty-four children, 7–16 years of age (11.12 ± 2.5), with CHD were age and sex matched to 25 typically developing peers. Anthropometric measures of height and weight were obtained. PA was assessed using the Physical Activity Questionnaire for Children/Adolescents and accelerometry. Dual x-ray absorptiometry (DXA) scans were obtained at the total body and peripheral quantitative computed tomography (pQCT) scans of the non-dominant radius and tibia were acquired. Independent sample t-tests were used to compare anthropometric and PA data. Multivariate analysis of covariance was used to compare DXA and pQCT measured bone mineral density (BMD), content (BMC), area, and estimated strength (pQCT only) between children with CHD and controls while controlling for: sex, age, height, weight, and PA levels.
Results
There were no differences in anthropometric measures and PA levels between children with CHD and controls ($P > 0.05$). Once age, sex, height, weight and PA were accounted for, there were no significant differences between children with CHD and controls in DXA measured total body aBMD, BMC and area ($P > 0.05$). Children with CHD had significantly lower total BMC (7%), cortical area (7%) and estimated strength (16%) at the tibial shaft ($P < 0.05$). There were no differences in the remaining pQCT variables ($P > 0.05$).
Conclusion
In contrast to previous research we did not find any difference in PA levels between children with CHD and their typically developing peers. Children with CHD had impaired bone parameters at the tibial shaft. Despite similar levels of PA children with CHD may have comprised bone strength at the tibia.
Disclosure
The authors declared no competing interests.

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P15

TA-46 prevents premature synchondrosis and restores foramen magnum size in a mouse model of achondroplasia

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Objectives
Achondroplasia, the most common form of short limb dwarfism, is a rare genetic disorder caused by a gain-of-function mutation of the FGFR3 receptor (FGFR3-G380R) and there are currently no effective treatments available. We have developed TA-46, a recombinant human soluble FGFR3(sFGFR3) form of the FGFR3 cell surface receptor containing an extra-cellular ligand-binding domain, including three IgG domains, which confer binding specificity. TA-46 is designed to block activation of the FGFR3-G380R receptor responsible for achondroplasia, thereby directly addressing the skeletal defect. TA-46 exerts its effects as either a ligand 'trap,' competing for the natural FGF ligands, or through formation of an inactive heterodimer with FGFR3 or FGFR3-G380R on the cell surface. To elucidate the potential therapeutic benefit of TA-46, we characterized its impact on skull synchondroses in a mouse model of achondroplasia carrying the mouse equivalent to the human G380R mutation (Fgfr3ach/+).
Methods
TA46 was injected subcutaneously at a dose of 10 mg/kg to newborn Fgfr3ach/+ mice – the mouse model of achondroplasia – twice per week throughout the growth period during three weeks. Longitudinal skull measurements were performed by X-rays were imaging at post-natal day 3, 9 and 22.
Results
Treatment with TA-46 compared with vehicle control prevented premature synchondrosis ossification and extended the period of bone formation in Fgfr3ach/+ mice. Treatment with TA-46 restored the foramen magnum to normal size and resulted in improved skull shape and cranium ratio. TA-46 was also associated with improved survival, body weight, and skeletal endochondral bone growth (body and tail length).
Conclusions
Given the impact of TA-46 on synchondrosis closure, it has the potential to prevent some of the most severe complications of achondroplasia if used early enough during bone development. These data support the clinical development of TA-46 for achondroplasia, and suggest that early treatment may be required to best address impaired endochondral bone growth.

Disclosure
Authors are employees and/or shareholders of Therachon, the company developing TA-46.

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P16

Higher neonatal bone mineral content and lower IL-6 levels in offspring of overweight/obese women following antenatal exercise: The IMPROVE randomized controlled trial (RCT)

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Objectives
The in-utero environment affects fetal development and health and disease risk in adulthood[1]. Maternal obesity during pregnancy is associated with low-grade inflammation and long-term offspring health risks[2]. Pro-inflammatory adipocytokines (TNF-α/IL-6) are linked with later obesity, insulin resistance and osteoporosis[3] 4, while low early-life bone mineral content (BMC) is associated with osteoporosis5. We assessed the impact of a moderate-intensity antenatal-exercise regime in overweight/obese pregnant women on offspring early-life metabolic markers, body composition and bone health.
Methods
The IMPROVE (Improving-Maternal-and-Progeny-Risks-of-Obesity-Via-Exercise) RCT was conducted in Auckland, New Zealand in non-smoking overweight/obese women (BMI $\geq$25 kg/m^2) aged 18–40 years, with singleton pregnancies. Participants were randomized to intervention/control groups stratified on ethnicity/parity. Intervention participants commenced home-based structured moderate-intensity exercise on stationary cycles at 20 weeks of gestation. Compliance was monitored by heart-rate monitors. Controls did not receive an intervention. Both groups received standard antenatal care, and completed diet-records and physical-activity questionnaires. Submaximal aerobic-capacity and metabolic markers were assessed at baseline and end-of-intervention (19 & 36 weeks gestation). Offspring assessments included cord blood metabolic markers, birth anthropometry and neonatal body composition (whole-body DXA scanning).
Results
Intervention group (n=38) and control group (n=37) had similar aerobic fitness, metabolic markers, dietary-intake and habitual-physical-activity levels at baseline. Intervention participants each completed an average of 22 (26-minute) sessions of prescribed exercise. Dietary-intake and habitual-physical-activity remained similar between exercisers and controls during the intervention-period. At end-of-intervention assessments, exercise participants had improved their aerobic fitness compared to controls (adjusted mean difference [aMD] test-time 48 s, P=0.02). Weight gain and metabolic markers were similar. Offspring birth anthropometry, lean-mass, fat-mass and BMD were similar, while exercise offspring had 20% higher BMC (aMD 9.1 g, P=0.01) and lower IL-6 levels in cord blood (aMD 14 pg/ml, P=0.03),compared to control offspring.
Conclusion
Antenatal exercise in overweight/obese women improved maternal aerobic fitness and demonstrated potential benefits on offspring health via lowered IL-6 and increased BMC.
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P17

Sex and maturation effects on trabecular and cortical microarchitecture in children and young adults

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The impact of sex and maturation on trabecular (Tb) and cortical (Ct) microarchitecture in children and young adults has not been well established. The new second-generation high-resolution peripheral quantitative CT (HR-pQCT) scanner (XCT II, Scanco Medical) incorporates three important advances to provide greater spatial resolution, direct measures of Tb thickness and spacing and measures in the Ct midshaft. The aim of this study was to identify sex and maturation effects on bone microarchitecture and to determine the impact of adjustments for IGF1 and leg muscle mass (LM) by DXA. This cross-sectional study included 286 healthy participants (148 females), ages 5 to 30 yrs recruited from the community and excluded from diseases or medications known to effect growth and bone health. The reference line was placed 2 mm proximal to the proximal margin of the growth plate (or growth plate remnant if fused) and scans were centered 3.5% (distal site) and 30% (proximal site) of tibia length proximal to the reference line. Log linear regression models were adjusted for age, age2, sex, tibia length and Tanner stage. At the proximal site, female participants had significantly greater Ct bone mineral density (BMD) and lower Ct thickness and porosity compared with males. Greater skeletal maturity was associated with greater Ct thickness, area and BMD independent of age and sex. Cortical porosity was markedly higher in pre-pubertal participants (an average of 5.3 and 4.0% in Tanner 1 males and females respectively, compared with 1.4 and 1.0% in Tanner 5). In the tibia metaphysis, greater maturation was associated with greater Tb thickness and the maturation effects were significantly more pronounced in males (significant sex-Tanner interaction). Tb number did not differ with maturation in males or females. After adjustment for IGF1 the sex and Tanner stage effects persisted and IGF1 was also positively correlated to trabecular number and thickness and cortical thickness and area at the proximal site. However, adjustment for LM eliminated sex and Tanner stage differences in these outcomes. In conclusion, the new XCT II device captures sex and maturation effects that were not evident with prior technology.
Disclosure
Andrew Burghardt's institution, UCSF, has research support by ultragenyx. Kyla Kent is a consultant for Ascendis Pharmaceuticals.

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P18

Bone mass and fracture prevalence in childhood brain cancer survivors (CBCS) 2 or 5 years after off therapy

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Background and aim
Multifaceted risk factors impair bone mass in childhood cancer survivors. Aims of the study were to evaluate bone mass and it's determinant and fracture prevalence in CBCS 2 (G+2) or 5 (G+5) years after off therapy (OT).
Methods
Seventy-three (G+2) and 87 (G+5) CBCS were evaluated at 12.9±4.2 and 14.9±4.4 yrs, respectively. Diagnoses were: astrocytic (G+2:n=25, G+5:n=24), embryonal (G+2:n=28, G+5:n=22), sellar region (G+2:n=13, G+5:n=10) tumors, germinomas (G+2:n=13, G+5:n=18), ependimomas (G+2:n=3, G+5:n=7). Growth hormone deficiency (GHD) was diagnosed in 38(G+2) and 67(G+5) pts, while hypogonadism (HH) in 23(G+2) and 34 (G+5) CBCS. Patients underwent height (cm, SDS), BMI (kg/m^2,SDS), pubertal (Tanner) and DXA (Lunar Prodigy Advance,GE) measurements. BMD(g/cm^2, Z-score), BMC(g) were obtained at the lumbar spine (L1–L4=L) and the total body less head (TB); lumbar BMAD (g/cm^3) was calculated; fat (FM%, Kg) and lean mass (LM, Kg) were obtained.
Results
G+2 and G+5 had comparable height (−0.5±1.3SDS), BMI (0.7±1.2SDS), FM (kg), LM (kg) and age at diagnosis (8.0±4.4yrs); G+2 showed a reduced LBMD and LBMC (P's=0.008 and 0.03, respectively) and a higher FM%

($P=0.04$) compared to G+5 and a non-significant lower LBMDZ-score (-0.85 ± 1.33 and -0.61 ± 1.23), BMAD (0.135 ± 0.021 and 0.154 ± 0.090), TBBMDZ-score (-0.72 ± 1.08 and -0.59 ± 1.04). A LBMD < -2Z-score was present in 19.2% and 11.5% (G+2 vs G+5) and a TBBMD < -2Z-score in 11.5% and 12.0% (G+2 vs G+5). G+2GHD pts had a lower LBMDZ-score ($P=0.008$) and TBDMDZ-score ($P=0.03$) compared to G+5GHD pts; G+2HH pts had a lower LBMDZ-score compared to G+5HH ($P=0.04$). In multivariable analyses LBMDZ-score was inversely predicted by age at study and directly by height in G+2 (R2 0.37) and G+5 (R2 0.23) after correction for LM, FM, GHD, HH; TBBMDZ-score was additionally predicted by LM in G+2(R2 0.57) and by LM and FM in G+5 (R2 0.54). Seven% CBCS in G+2 (5/72) and 2.3% in G+5 (2/86) presented fractures.

Conclusions

Older, shorter, GHD and HH CBCS are at risk of decreased bone mass after 2 yrs OT; a low bone mass might persist after 5 yrs OT; however, the fracture prevalence remains low.

Disclosure

The authors declared no competing interests.

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P19

Progresive-deforming form of osteogenesis imperfecta in neonates – own experience

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Fractures of long bone and ribs in the neonatal period may be expression of genetic disturbances of collagen type I production. The aim of the study was to present clinical symptoms, laboratory, radiological and densitometric data in 27 newborns with osteogenesis imperfecta type III.

Methods

Medical history, clinical examination and radiographs of 27 children hospitalized in the Department of Paediatrics, Neonatal Pathology and Bone Metabolism Diseases were evaluated. Serum levels of 25-hydroxyvitamin D (25OHD) and osteocalcin (bone formation marker) of the patients were measured. Assessment of urine excretion of bone resorption marker D-Pyrylinks was made. All of the newborns were qualified to pamidronate therapy and the treatment was commenced. After the first cycle of pamidronate, densitometric examination in Infant programme by dual-X-Ray absorptiometry (DXA method) was performed.

Results

In every family of evaluated patients osteogenesis imperfecta occurred by the first time. In clinical examination the disease was manifested by deformations in body proportions: shortened extremities, sabre shanks, flabby skull bones and reduction in activity. 23 of 27 children had blue sclera. In all X-ray baby-graphs bone fractures, developed in utero as well as after birth, were found. From biochemical tests only a few abnormalities were observed, such as lowered concentration of serum 25OHD in 9 of 27 patients. Due to orthopedic care of the multiple fractures DXA method is hard to obtain during first hospitalization, so that it is performed before second cycle of pamidronate.

Conclusion

1. Osteogenesis imperfecta is one of the reasons of bone fractures in neonates and its diagnosis is based on family history, clinical manifestation and X-ray examination.
2. Based on our experience Dual X-ray absorptiometry is useful for the pamidronate therapy monitoring, not for making the diagnosis of osteogenesis imperfecta.

Disclosure

The authors declared no competing interests.

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P20

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P21

Efficacy and safety of intravenous infusión of ibandronic acid in children with osteogenesis imperfecta

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Introduction

Osteogenesis Imperfecta (OI) in children has been treated with different types of biphosphonates between which Pamidronate has been the most used. Zolodronic acid has shown igual efficacy, but few studies have used ibandronic acid infusion in children.

Objective

To show efficacy and safety of ibandronic acid infusión in preventing fractures in children with OI.

Methods

12 children with ages between 2 and 6 years were included in the study. They were receiving therapy with pamidronate infusions three days every 3 months for the last 3 years. They were switched to ibandronic acid intravenous infusión 0.15 mg/kg body weight once every three months. Vitamin D and calcium supplements were given as before. Patients were monitored for side effects during and after the infusions and also for the incidence of fractures before and after the change of therapy for 18 months

Results

No side effects were registered during or after the infusión. During the period of observation for 18 months only one patient showed a fracture as he fell from his bed, the other patients did not present any fracture. Levels of calcium and vitamin D were normal before and after the therapy.

Conclusion

Ibadndronc acid infusion is as safe and offices as pamidronate therapy in preventing fractures in children with OI. Being only one day of application instead of three, it can be easier both for patients and for parents giving the same efficacy.

Disclosure

The authors declared no competing interests.

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P22

Tibia microarchitecture in children with recent fractures

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Objectives

Children who fracture have lower bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA) than children who do not sustain fractures, but there is little data on bone microarchitecture in relation to childhood fracture. We assessed tibia microarchitecture using high resolution peripheral quantitative computed tomography (HR-pQCT) in children with recent fracture and those without a history of fracture.

Methods

Children age >10 years with a confirmed low/moderate impact fracture in the preceding 6 months were compared to controls with no history of fracture. Distal tibia microarchitecture was assessed using HR-pQCT (XtremeCT, Scanco Medical AG, Switzerland). Standard deviation scores (SDS) for age, sex and ethnicity were calculated using published reference data (Gabel 2018 doi:10.1002/jbmr.3399) for total volumetric BMD (Tt.BMD), cortical thickness (Ct.Th), cortical volumetric BMD (Ct.BMD), trabecular number (Tb.N), trabecular thickness (Tb.Th) and trabecular bone volume (BV/TV). Results are presented as mean [SD].

Results

33 children with fractures [F] (age 13.5 [1.6] years; 73% male) were compared with 35 non-fracturing controls [C] (mean age 13.1 [2.0] years, $P=0.33$; 67% male, $P=0.61$). Children with fracture had similar Tt.BMD SDS (1.23 [1.11]) to controls (1.05 [1.47], $P=0.57$). Trabecular microarchitecture was similar between the groups (Tb.Th SDS C: 0.32 [1.31] F: 0.32 [1.04], $P=0.99$; Tb.N SDS C: -0.01 [1.41] F: 0.14 [1.22], $P=0.63$; BV/TV SDS C: -0.50 [1.14] F: -0.37 [1.19], $P=0.63$). SDS for Ct.Th (C: 0.91 [1.68] F: 1.09 [1.21], $P=0.60$) and

Ct.BMD (C: 3.41 [1.88], F: 3.09 [1.16], $P=0.40$) also did not differ. Inclusion of only children with long bone fractures ($n=22$) did not alter the findings, nor did analysis of boys and girls separately. 9 children with fractures had a previous confirmed fracture. Tibia microarchitecture did not differ in these children compared to those with only a single fracture ($n=23$) or non-fracturing controls ($P>0.05$ for all).
Conclusions
Bone microarchitecture at the tibia was not different in children with a recent fracture to those without a history of fracture.
Disclosure
The authors declared no competing interests.
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P23

What happens to the skeleton at the time of diagnosis of paediatric cancer?
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Objectives
To evaluate the skeletal profile of paediatric patients with cancer at diagnosis.
Methods
Children diagnosed with cancer in our Oncology Centre were recruited during a fifteen-month period and underwent metabolic bone profile and dual-energy X-ray absorptiometry (DXA) at the time of diagnosis. Subsequently, they were divided in two subgroups, according to diagnosis; haematological malignancy vs solid tumour. For comparison, a group of 38 sex and age-matched controls was used.
Results
Sixty-nine children were recruited (41 boys, 50 prepubertal), aged 7.6 ± 4.6 years. Of those, 39 were diagnosed with haematologic malignancies and 30 with solid tumours. Eighteen out 69 patients had bone pain, fourteen had a limp and one sustained a femoral fracture. 45% of the patients were vitamin D insufficient (25–OH-D: 12–20 ng/ml) and 7.2% were deficient (<12 ng/ml). There was no difference compared to controls or between the subgroups. Hyperparathyroidism was present in 10% and hypercalciuria in 28% of all patients. Bone turnover was also affected, particularly bone formation, because the patients had lower levels of osteocalcin (OC, $P<0.001$) and procollagen type I propeptide (PICP, $P=0.003$), compared to controls. Within-group analysis revealed lower bone formation markers in the haematological subgroup i.e. OC and PICP ($P=0.003$ and 0.01, respectively), whereas the solid tumour subgroup had higher bone resorption markers, ie tartrate-resistant acid phosphatase ($P=0.02$) and urine deoxypyridinoline/urine creatinine ($P=0.005$). Finally, a DXA scan was performed in 38 patients; 20% of them had low-normal bone mineral density (BMD) of the lumbar spine (LS Z-score between -1 and -2) and only one patient had low BMD Z-score <-2 at the same site. Total body less head scans (TBLH) were normal. Patients with haematological malignancy had lower BMD, with a more pronounced reduction at the lumbar spine ($P=0.03$), compared to those with solid tumour.
Conclusion
Skeletal health is already adversely affected at the time of diagnosis of paediatric cancer. Low vitamin D is common. Bone turnover is disturbed and follows different patterns, depending on the type of the tumour. Finally, BMD reduction is more pronounced in haematological malignancies. These observations support bone health surveillance and intervention at the time of cancer diagnosis.
Disclosure
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P24

The role of the RACK1-c-Src axis in regulation of osteoclast function
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Activation of p38 MAPK by RANKL is regulated by the scaffolding protein receptor for activated C-kinase 1 (RACK1) in osteoclast precursors, whereas it is unclear whether RACK1 can also affect in mature osteoclasts. In this study, to identify that the interaction of RACK1 with c-Src is essential for osteoclast function, we generated several mutants affecting the RACK1-c-Src association. A RACK1 mutant protein (mutations of tyrosine 228 and 246 residues to phenylalanine) disrupted interaction with c-Src and significantly decreased the phosphorylation level of c-Src. Furthermore, the mutant impaired the integrity of actin cytoskeleton and bone resorption activity of osteoclasts. Remarkably, Lysine 152 within the SH2 domain of c-Src is an important residue of interaction between RACK1 and c-Src. The bone-resorbing activity of osteoclasts is diminished by the c-Src K152R mutant (mutation of lysine 152 into arginine). These findings suggest that RACK1 plays a critical role in regulating osteoclast function through its ability to interact with c-Src and modulate its activity, which will help to develop new anti-resorptive therapies for preventing bone loss-related diseases.
Disclosure
The authors declared no competing interests.
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P25

Short term mechanical stimulation using whole body vibration identifies differences in bone response between prepubertal boys with and without prior fracture
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Objectives
Previously we have shown in healthy pre-pubertal boys that short periods of whole body vibration (WBV) increased the bone formation marker PINP by 25.1% and resorption marker CTX by 10.9%. The aim of this study was to see if otherwise healthy boys with a history of fracture would respond to WBV in the same way.
Methods
In addition to 11 pre-pubertal boys measured previously in the same way, 20 pre-pubertal boys aged 7-13 years, who were at least 6 months post fracture, were randomised to stand on either the Juvent 1000 (low magnitude, high frequency) or the Galileo Med M (high magnitude, high frequency) platforms for 10 minutes (2.5 minutes $\times$ 4 with interspersed 30 second rest periods) on 5 consecutive days. Fasting serum was collected before WBV on D1 and on D8. PINP and CTX were measured using an automated analyser and OPG and sclerostin using manual ELISAs.
Results
PINP and CTX increased from baseline to D8 in the non-fracture boys ($n=11$; 743 (189) to 894 (277) ng/ml and 1.876 (0.389) to 2.046 (0.506) ng/ml respectively), but did not change in the boys with a history of fracture ($n=15$; 588 (156) to 578 (172) ng/ml and 1.951 (0.341) to 1.922 (0.467) ng/ml respectively). The differences in %change of P1NP and CTX between the non-fracture and fracture groups were highly significant; mean difference in PINP %change was 23.8% (CI 10.8 to 36.9; independent samples t-test $P=0.001$); mean difference in CTX %change was 11.8% (CI 1.7 to 21.8; $P=0.02$). Multivariate analysis including a range of other factors such as body size and physical activity made no difference to the results. There were no significant changes in OPG or sclerostin from baseline at D8 in either group. No difference between platform groups was found.
Conclusions
Boys who have a history of fracture show reduced responsiveness to short periods of WBV compared to non-fracturing counterparts; reduced responsiveness to mechanical stimulation, if present prior to the fracture occurring, and if related to reduced bone accrual, might help explain increased fracture susceptibility in some children.
Disclosure
NJB consults for Alexion, Mereo, UCB and Amgen, and receives grant support for clinical studies from Alexion and Amgen.
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P26

Parathyroid hormone is higher in infants with fracture as opposed to without fracture undergoing skeletal survey for suspected non-accidental injury, and is inversely associated with mean corpuscular haemoglobin content

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Background
Biochemical and haematological testing is recommended in the United Kingdom when non-accidental injury is suspected. We examined the associations of test results with radiologically-confirmed fracture(s), and between test results, in a retrospective observational cohort.
Methods
Infants up to age two years presenting with suspected non-accidental injury, without clinically-apparent bone disease, and where a skeletal survey was undertaken during the period 1st August 2013 to 31st July 2017, were included. Biochemical parameters: corrected calcium (cCa); phosphate (P); alkaline phosphatase (ALP) all measured by dry slide on the Ortho-Clinical Diagnostics Vitros 5·1 analyser; parathyroid hormone (PTH) by a CMIA method on the Abbott Architect i1000; 25-hydroxyvitamin D (25D) by liquid chromatography tandem mass spectrometry; and haematological parameters using a Siemens Advia 2120: haemoglobin (Hb); mean corpuscular haemoglobin (MCH); mean corpuscular haemoglobin content (MCHC); mean corpuscular volume (MCV); platelet count were collated together with the results of the radiological assessments. Radiographs were reported by experienced paediatric radiologists.
Results
Of 185 eligible infants (68 male), 67 (27 male) had one or more fractures. Mean PTH in the fracture and non-fracture groups was 51.1 and 31.6 ng/l respectively; difference 19.5 ng/l, 95%CI 0.7–38.3 ng/l, $P=0.0420$. The factors which in combination were most strongly associated with PTH were (in order of strength of association) ALP (positively), cCa (negatively), age (negatively), MCHC (negatively) and fracture (positively). The coefficient for fracture in the determination of PTH from the regression analysis (19.4 ng/l) was similar to the unadjusted analysis comparing the fracture and non-fracture groups. There was no clear association of PTH with timing in relation to fracture.
Conclusions
PTH was raised in infants who had fractured compared to those who had not; PTH was negatively correlated with MCHC suggesting a possible relationship of PTH with iron sufficiency. Further studies are needed to clarify the relationships of PTH, 25D and MCHC with fracture; it is unclear if PTH was increased before or after fracture occured. Interpretation of data from biochemical and haematological testing should be informed by the overall presentation in suspected non-accidental injury cases.
Disclosure
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P27

Response to mechanical stimulation of bone in children with osteogenesis imperfecta and the effect of bisphosphonate therapy

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Objectives
Children with osteogenesis imperfecta (OI) suffer fragility fractures due to altered bone mass, architecture and material quality. Management is multidisciplinary, often including bisphosphonates and physiotherapy. We wished to determine whether bisphosphonates altered the skeletal response to mechanical stimulation in OI. Short term exposure to whole body vibration (WBV) in apparently healthy children results in increases in bone formation and resorption markers, providing a dynamic test of the acute skeletal response to mechanical stimulation.
Methods
12 children with OI, naïve to bisphosphonate treatment, stood on a high frequency low amplitude vibrating platform (LivMD) for 10 minutes daily (2.5 minutes × 4 with interspersed 1 minute rest periods) for 7 days, followed successively by five weeks 'washout', six weeks of risedronate treatment and one week of WBV. P1NP, alkaline phosphatase and CTX were measured at baseline and at intervals bracketing the periods of vibration and risedronate treatment.
Results
There were statistically significant increases in predicted P1NP ($P=0.019$) and CTX ($P=0.013$) but not alkaline phosphatase ($P=0.11$) by repeated measures ANOVA across the whole period of the study. Both P1NP and CTX rose after the initial WBV period (D1 –D8); P1NP from 442.8 to 529.1 ng/ml, $P=0.016$; CTX from 1.256 to 1.437 ng/ml, $P=0.023$. P1NP and CTX values decreased following treatment with Risedronate (D43 –D85); P1NP 534.9 to 438.2 ng/ml $P=0.006$ and CTX 1.507 to 1.253 ng/ml $P=0.002$. P1NP and CTX changed less after the second period of vibration; P1NP 438.2 to 454.2 ng/ml $P=$NS; CTX from 1.253 to 1.376 ng/ml $P=$NS. P1NP increased significantly more from D1-8 then from D85-92; %change 16.3 vs 3.5% $P=0.016$; there was no significant difference in the change in CTX between the two time periods.
Conclusions
The initial change in biomarkers following WBV shows bone tissue in children with OI is capable of responding to mechanical stimulation. Both P1NP and CTX fell following risedronate treatment, and increased less subsequently in response to mechanical stimulation. These data suggest there is some reduction in skeletal responsiveness to mechanical stimulation following bisphosphonate treatment that has implications for the management of these children.
Disclosure
NJB consults for Alexion, Mereo, UCB and Amgen, and receives grant support for clinical studies from Alexion and Amgen.
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P28

Duchenne muscular dystrophy: preliminary results of the Risbo-DMD study

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Introduction
Reduced bone mineral density [BMD] and increased fracture risk are common complications in all conditions characterized by severely reduced physical activity and/or requiring long-term glucocorticoid [GC] treatment, including Duchenne Muscular Dystrophy [DMD].
Objectives
The RisBo-DMD study (EudraCT 2011-005745-12) is a 24-month prospective multicenter study, aimed at identifying DMD patients at higher risk of fractures and improving the bone treatment strategy.
Methods
At baseline, 12 and 24 months: DXA spine (LS) and total-body-less-head (TBLH) bone mineral density [BMD] measurement; spine X-rays for vertebral fractures; biochemical tests for bone metabolism, including bone turnover markers (CTx, NTx, OC, BAP) and bone-related cytokines (RANKL, OPG, DKK1, IL6). Months 1-12-24: all patients treated with calcifediol (0.8 μg/kg/die) and instructed to adequate dietary calcium intake to the RDA. 12-month assessment: Patients at 'high risk' of fractures identified based on: baseline BMD Z-score ≤ -1.5; history of previous fractures; incident fractures; increased bone resorption markers for age; BMD yearly increase $\leq 5\%$. Months 12–24: patients at high risk of fractures treated with i.v. zoledronate infusion every 3 months (first dose 0.0125 mg/kg; subsequent doses 0.025 mg/kg).
Results
54 patients were enrolled. At baseline evaluation, we observed low spine BMD (Z-score -2.19 ± 1.10); intermediate levels of serum 25-OH D (39.5 ± 27.9 ng/ml); high levels of bone resorption markers (serum CTx 721.7 ± 323.9 pg/ml; urinary NTx 498.7 ± 439.1 nMBCE/mMCrea). After 24 months, there were 3 appendicular and 2 vertebral fractures in patients not treated with bisphosphonate, while no incident fractures in patients treated with zoledronate. We observed a general improvement in both LS and TBLH BMD and in LS BMC ($P<0.001$ for all), while the LS Z-score increased (-0.85 ± 2.76; NS) only under zoledronate. General increase in 25-OH D levels (57.36 ± 34.21 ng/mL; $P=0.0025$) and reduction of NTx (352.24 ± 386.5 nMBCE/mMCrea; $P<0.001$) were found, while only in the zoledronate-treated group CTx and OC decreased (233.1 ± 195.7 pg/mL, $P=0.02$; 18.1 ± 13.5 ng/ml, $P=0.0099$).

Conclusions
These results indicate that adequate dietary calcium intake plus calcifediol is a valuable first-line treatment to improve bone metabolism in GC-treated DMD patients. The addition of zoledronate in patients with more severe bone alterations and a higher risk of fractures is a further improvement.
Disclosure
The authors declared no competing interests.
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P29

Rib cage anomalies in a cohort of osteogenesis imperfecta patients
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Osteogenesis Imperfecta (OI) is a rare congenital disorder of bone fragility. Majority of OI cases are caused by loss of function or missense pathogenic variants in the COL1A1/2 genes. In addition to fractures, patients suffer from different, mainly long bone, skeletal deformities. OI patients might develop chest deformities (pectus carinatum (PC) or excavatum (PE)) of different severity, which can tend to formation of cardiopulmonary complications. The main aim of current study was to investigate chest deformities in 165 patients from the OI database of Tartu University Department of Traumatology and Orthopedics. We have compared severity of the chest deformity with OI type, genotype and sex of the patient. Data of OI genotypes was recruited from previous Sanger sequencing mutational analysis of the COL1A1/2 genes. Chest deformity was examined with observation. Significance of correlations was confirmed with Fisher's test. 55.65% (92/165) of patients suffered from moderate to severe chest deformities. Severity of deformation correlated with OI type (P-value = 0.0002e-12). Chest deformities did not reveal correlation with affected gene (P-value = 0.7205) or sex (P-value = 0.183). However, among COL1A1/2 cases, severity of the chest deformity depended on the collagen defect type (P-value = 0.0006). Extreme chest deformities were present in 22.82% (21/92) cases. Four (19.05%) of them were PE (all present in male patients) and 17 (80.95%) PC (9 males and 8 females). Out of non-COL1A1/2 OI cases, all patients with extreme chest deformities were OI type 3. Among collagen OI cases were types 1 (PE), 3 (PE, PC) and 4 (PC). Especially severe PC cases were caused by following mutations: COL1A1 c.1981G>C p.(Gly661Ser), COL1A2 c.792+1G (haploinsufficiency), COL1A1 c.1350G>C p.(Glu450Asp). In contrast to cases of PE and PC of unknown etiology, OI-related PE and PC do not correlate with sex. Chest deformities arise with similar frequency among collagen-related and non-COL1A1/2 OI patients. More severe chest deformities were common among OI type 3 patients, and patients with missense, compared to loss of function COL1A1/2 pathogenic variants. Despite carrying of the same OI pathogenic variant, development of the PE and PC differs among patients, what underlines presence of additional factors affecting rib cage deformity development in OI patients.
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P30

Bone mass, sclerostin and body composition in women with anorexia nervosa: a 3-year follow-up after weight gain therapy
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Objectives
Patients with anorexia nervosa (AN) are at high risk of reduced bone mass. The aim of this intervention study was to investigate the long-term effects on bone and body composition three years after intense weight gain therapy.
Methods
Twenty-five female AN patients, mean age 20.1 years, mean BMI of 15.5 kg/m^2, were included. Twenty-two patients fulfilled the treatment for 12 weeks with a high-energy diet. Body composition and bone mass were assessed by dual-energy X-ray absorptiometry and peripheral quantitative computed tomography at start, 12 weeks and 20 patients were evaluated after 3 years. Serum sclerostin was assessed by ELISA.
Results
During the 12 week therapy, mean BMI increased from 15.5 to 19.0 kg/m^2, $P<0.001$, and remained stable during 3 years. Fat mass increased from 14.0% to 26.3% during the intervention period and remained stable over 3 years. Lean mass was unchanged during the study period. The mean fat/muscle area was 22.7% at baseline and increased to 31.7% after 12 weeks therapy, $P<0.001$, and remained stable over 3 years. The mean baseline values were, for total body BMD 1.1 g/cm^2, lumbar spine BMD 1.0 g/cm^2, lumbar spine BMC 53.8 g, which did not change over the study period. Total body BMC, 2195 g at baseline, increased to 2287 g during the 12-week intervention ($P=0.002$) but decreased after 3 years to 2215 g ($P<0.05$). The mean tibial trabecular density (4%) was 237 mg/cm^3 at baseline and decreased to 222 mg/cm^3 after 12 weeks, $P<0.001$, which further decreased to 207 mg/cm^3, $P=0.01$. The mean tibial cortical density (66%) was 1153 mg/cm^3 at baseline and was unchanged over 3 years. The highest level of sclerostin was observed at baseline, mean 30.1 pmol/l, which decreased after 12 weeks and 3 years to 27.1 pmol/l and 21.7 pmol/l, respectively, $P<0.05$.
Conclusion
Tibial trabecular density decreased even though areal BMD was unchanged. The reduction in sclerostin implies a possible compensatory mechanism to increase bone formation on the cellular level. This study indicates the importance of long-term follow-up of bone health in young women with severe AN, although stable BMI values were achieved.
Disclosure
The authors declared no competing interests.
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P31

Determinants of survival in osteogenesis imperfecta (OI) Type II
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Introduction
In 1979 Sillence described Type II OI as perinatal lethal. We report two children whose features were consistent with Type II OI who survived beyond infancy. Both have mutations previously reported in cases of lethal OI.
Case 1
This girl was born full term, small for gestational age (SGA) following antenatal detection of short bowed femora. Skeletal survey showed multiple long bone fractures and a small chest with beaded ribs. A COL1A2 gene (c.1774 G>A in exon 31) mutation was identified. Following discharge at two weeks of age she was readmitted for respiratory infection, requiring long term non- invasive ventilation (NIV) from age five months. She developed raised intracranial pressure (ICP) due to basilar invagination, with hydrocephalus and cerebellar tonsillar herniation requiring ventriculo-peritoneal shunt insertion. At the current age of 2 years, she continues on NIV at home, has severe growth impairment (z scores: height −6.87, weight −4.63, head circumference −1.16).
Case 2
This boy was born full term SGA. Femoral bowing was demonstrated on antenatal ultrasound. Clinical and radiological features were similar to Case 1. He has a mutation in COL1A1 gene (c.3150_3158 dup in exon 44). He required ventilation from age 4 days and remains dependent on long term NIV. He developed raised ICP at four months due to bilateral subdural hematomas requiring subdural peritoneal shunt insertion. He was an in-patient until 11 months of age. At age 18 months he has severe growth impairment (z scores: height −9.81, weight −5.21, head circumference −1.61). Both children received two-monthly Pamidronate (0.75 mg/kg/day for two days) infusions, initiated in the first week of life. They received intensive support from the multidisciplinary OI team. Since discharge on NIV neither child was readmitted for significant respiratory infections. Both children have severe skeletal deformities and have had a single post natal long bone fracture. They have severe cognitive and motor delay and have not achieved head control yet.

Conclusions
The key determinants of survival in these children were respiratory support and neurosurgical intervention with multidisciplinary team support. Neurosurgical complications should be anticipated in this group and screening neuroimaging is advised.
Disclosure
The authors declared no competing interests.
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P32

Successful use of oral acetazolamide in symptomatic subcutaneous calcifications in hyperphosphatemic tumoral calcinosis
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Introduction
Hyperphosphatemic familial tumoral calcinosis is a rare genetic disorder causing reduced FGF23 activity. Recurrent and occasionally disabling subcutaneous calcifications are major disease manifestations. We describe the successful use of acetazolamide in two cases presenting in childhood with a homozygous GALNT3 mutation.
Case 1
A five year old girl developed tender subcutaneous calcifications in the right elbow which were surgically resected. A year later, she presented with painful new calcifications around the left elbow associated with acute inflammation.
Case 2
A 2.5 year old girl presented with subcutaneous calcifications in her right elbow which were surgically resected on two occasions, with recurrence of tender lesions at 5 years of age at the same site, this time with an additional new large, inflamed lesion in the left hip. Both cases were of African origin with unaffected family members.
Biochemistry: Typical biochemistry with elevated serum phosphate 2.1–2.4 mmol/L (0.9–1.8 mmol/L) but normal calcium, alkaline phosphatase and parathyroid hormone levels noted in both cases.
Management: Acetazolamide was commenced at 20 mg/kg per day in two divided doses. Treatment was monitored with weekly blood gas analysis, aiming for a bicarbonate levels of 16–19 mmol/L. Acetazolamide was reduced to 15 mg/kg/day in Case 1 and increased to 35 mg/kg/day in case two over eight to ten weeks. Case 1 was managed with acetazolamide monotherapy. Case 2 was initially started on sevelamir which was continued, with addition of acetazolamide and topical 25% metabisulfite.
Treatment response
Substantial resolution of pain and swelling was noted both clinically and radiologically by 12 weeks of commencing oral acetazolamide. No significant adverse effects were reported. Clinical effects were sustained at one year in Case 1 and two years in Case 2 at last follow up.
Conclusion
Oral Acetazolamide is a well-tolerated and effective treatment option in children with subcutaneous calcifications in hyperphosphatemic tumoral calcinosis.
Disclosure
The authors declared no competing interests.
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P33

Unusual case of severe hypophosphataemic rickets and renal stones associated with valproate use
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Background
Hypophosphataemic rickets has been reported in patients on long term sodium valproate. This is usually due to proximal renal tubulopathy (RT). Distal RT or renal stones have not previously been reported.
Presenting problem
We report the case of a 6 year old female with complex background (severe global developmental delay, epilepsy, PEG fed), on long term sodium valproate, who developed chronic hypophosphatemia and sustained a low impact femoral fracture. She developed severe hypocalcaemia following use of intravenous magnesium sulphate for respiratory symptoms. Further investigations showed bilateral renal stones, florid rickets, and mixed proximal and distal RT.
Clinical management
Bloods on admission showed severe acute on chronic hypophosphataemia (0.37 mmol/L, reference range 1.36–2.26), raised ALP (3000 iu/L, reference range 177-1036), normal calcium, PTH and vitamin D levels. Following magnesium infusion, calcium level dropped (A Ca 1.34 mmol/L, reference range 2.20–2.79). Calcium infusion caused a further drop in phosphate (0.22 mmol/L, reference range 1.36–2.26), and treatment with phosphate led to a PTH rise (32.2 pmol/L, reference range 1.1–6.9). Bloods demonstrated hyperchloraemic acidosis with low bicarbonate (15 mmol/L, reference range 18–29), and high chloride (113 mmol/L, reference range 100–110). Radiographs showed features in keeping with florid rickets. Urine sample showed alkaline urine (pH 7.5) with proteins, amino acids, increased calcium/creatinine ratio (1.52 mm/mm, reference range 0–0.7) and citrate/creatinine ratio (2.2 mm/mm, reference range 0.11–.055) and a low tubular reabsorption of phosphate (TmP/GFR 0.68). DMSA scan was suggestive of proximal RT and a renal ultrasound revealed bilateral renal stones, which are usually associated with distal RT. Treatment with phosphate, calcium and alfacalcidol helped in normalizing bone biochemistry. She was gradually weaned off sodium valproate and changed to levetiracetam. Calcium and phosphate supplements were weaned and stopped subsequently. Repeat bone profile and x-rays after 3 months showed a complete resolution of radiological signs of rickets and a normal bone profile.
Discussion
Sodium valproate is known to cause proximal RT. Our patient had features of mixed proximal and distal RT which to our knowledge has not been reported before. RT, abnormal bone biochemistry and radiological rickets resolved after stopping sodium valproate medication.
Disclosure
The authors declared no competing interests.
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P34

Bone metabolism and bone mineral density in Duchenne muscular dystrophy
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Duchenne muscular dystrophy (DMD) is associated with an increased risk of bone fragility due to the adverse effects of prolonged glucocorticoid therapy and progressive muscle weakness on bone strength. The resultant osteoporosis, which predisposes to fragility fractures of both long bones and vertebrae, is a major cause for concern. We studied 70 boys with DMD mean age 10.74 ± 3.83 years. Bone mineral density was measured by DXA scan on lumbar spine and total body and content Z-scores adjusted for age, gender and height. Diagnosis of osteoporosis was made according to International Society for Clinical Densitometry 2013 criteria. Evaluation of calcium, phosphorus, alkaline phosphatase content and calciotropic hormones was performed. 48 patients were treated with steroids (23- deflazacort; mean dose 0.34 mg/kg, 25 with prednisone; mean dose 0.3 mg/kg). Bone mineral density (BMD) was lower than normal for age in all patients, and even lower in the group of steroid-treated children. Children with normal BMD were significantly younger, compared to those with decreased BMD (9.636 ± 3.33 vs 12.89 ± 3.13 years, $P < 0.001$). Past medical history of 18 patients (44%) revealed a bone fracture, 66% of them referred to the lower extremities. Osteoporosis was diagnosed in 15% od patients. Majority patients (64) were supplemented with vitamin D. Mean dose was 1895,6 IU/day (400–6000 IU). There was no significant difference in dose of supplemented vitamin D between ST−/+ groups. In 30% of studied patients serum concentration of vitamin D was below 20 ng/ml, and in 67% was below 30 ng/ml. Comparing blood results between children ST−/+ the only significant difference was in Alkaline phosphate activity (135.62 ± 42.85 U/l vs 114.52 ± 35.77 U/l, $P = 0.038$), the remaining: 25OHD (23.10 ng/ml vs 25.7 ng/ml; $P = 0.09$), PTH NS (16.8 vs 19.7 pg/ml), calcium NS (9.61 mg/dl vs 9.78 mg/dl; $P = 0.06$), phosphorus NS (4.54 mg/dl vs 4.64 mg/dl). In conclusion, decreased bone mineral density was present in DMD patients, and were worsening during corticosteroid therapy. It is thus recommended that bone and mineral metabolism be carefully evaluated in patients with DMD, so that appropriate measures could be taken, especially now that chronic corticosteroid therapy is frequently given
Disclosure
The authors declared no competing interests.
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P35

Atypical fractures in pediatric patients with osteogenesis imperfect treated with zoledronic acid

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Overall objective
To describe the incidence and relationship between the period of application of zoledronic acid and the presence of atypical diaphyseal fractures and subtrochanteric pattern in pediatric patients with osteogenesis imperfecta in the Mexican population.
Method
Type of study: Ambispective cohort in pediatric patients with a diagnosis of osteogenesis imperfecta. Prognostic variable: duration of treatment with AZ Outcome variable: presence of atypical fractures.
Eligibility Criteria
1. Patients with a clinical diagnosis of osteogenesis imperfecta
- That they are being treated with zoledronic acid.
- With complete radiographic file.
- With control densitometry
- That they have a complete clinical history, including a description of bone health.
- With initial laboratories of vitamin D and serum calcium.

Monitoring methods
- X-rays in anteroposterior and lateral views of the thigh, hip every 6 months, these radiographs will be studied by two pediatric orthopaedists
- Densitometry every 6 months
- Laboratory studies serum calcium, albumin, PTH and vitamin D, PIN, CTX every 6 months
- Bone health questionnaire every 6 months

Results
Retrospective phase: We studied 26 patients with a mean age of 10 years, 17 men, 9 women, 10 patients with type I OI, 13 patients with type III OI and 3 patients with type IV OI found in the radiographic record, 5 patients with atypical fractures in the region. subtrochanteric with an average of 6 times AZ application
Prospective phase
Twelve patients were followed, with a mean age of 10.2 years, 7 men, 5 women, 7 patients with type I OI, 3 patients with type III OI and 2 patients with type IV OI, with vitamin D levels of insufficiency (less than 30 ng/ml). To date, 5 atypical fractures have been found, 1 patient with OI type IV after 3 applications, and a patient with OI type III with 18 applications, 2 patients with OI type I with 10 applications, and 1 patient with OI type I with 6 Applications.
Conclusions
After finding the atypical fracture, we suspend the treatment for 6 months, finding regeneration of the fracture zone.
Disclosure
The authors declared no competing interests.

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P36

ALPL gene mutation in a family

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Introduction
The clinical diagnosis of mild forms of hypophosphatasia [HPP], a rare genetic bone disease, is often made in adulthood, on the basis of persistently low serum levels of alkaline phosphatase [ALP], often coupled with signs of poor bone/teeth mineralization.
Case report
A 50-year-old male on treatment with vitamin D supplementation because of osteoporosis of lumbar spine (T-score –3.2) and femoral neck (T-score –2.4), was referred to our Center after radiological evidence of vertebral fractures, and the finding of persistently low ALP levels (27 to 29 U/L). He reported episodes of stiff neck, tingling, and upper limb paresthesias. Ultrasound revealed tendon calcifications, and lab tests confirmed persistently low levels of ALP and high levels of 25-OH vitamin D (86 ng/ml). A diagnosis of HPP was thus suspected and genetic tests were requested.
Objectives
Molecular analysis of the ALPL gene to confirm the clinical diagnosis of HPP, to be extended, as appropriate, to the patient's relatives.
Methods
ALPL (NM_000478.4) sequencing was performed at our laboratory by Next Generation Sequencing [NGS] technology (MySeq Illumina).
Results
The coding sequence of exon 12 of our patient revealed the c.1328C>T (p.A443V) variant in heterozygous form – a mutation already reported in HGMD Professional 2015.3 and in the ALPL gene mutation database (http://www.sesep.uvsq.fr/03_hypo_mutations.php), and associated to HPP. This confirmed the diagnosis of HPP (which required a substantial reduction of vitamin D supplementation). Upon this finding, we performed genetic analysis in our patient's three daughters (respectively aged 8, 13 and 16 years), and the same genetic variant was found in the two youngest daughters. Their clinical history revealed appendicular fractures (1 and 2 respectively), and low serum levels of ALP for age (100 and 31 U/L respectively).
Conclusions
Genetic analysis is essential to confirm the diagnosis of mild forms of HPP. In this case, extending the analysis to our patient's daughters allowed us to make an early diagnosis of mild HPP in two more subjects.
Disclosure
The authors declared no competing interests.

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P37

Generation of osteogenesis imperfecta type XIV zebrafish models

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Objectives
Osteogenesis Imperfecta (OI) type XIV is a recessive OI form characterized by bone fragility, multiple fractures and growth retardation. It is caused by mutation in TMEM38B gene encoding the endoplasmic reticulum (ER) channel TRIC-B. This channel allows the transport of K+ across the ER membrane modulating Ca2+ flux. Defective ER Ca2+ impaires collagen type I synthesis, likely affecting the activity of ER enzymes involved in its post translational modification. To investigate the role of TRIC-B in skeletal development an in vivo model of the disease will be of great relevance. Since OI type XIV murine model is lethal at birth, zebrafish could be an interesting alternative to study this heritable skeletal disease.
Methods
Temporal and spatial distribution of zebrafish tmem38b during development was evaluated by qPCR and *in situ* hybridization. To generate a zebrafish model for OI XIV we used CRISPR/Cas9 system. tmem38b gRNA and Cas9 mRNA were injected in fertilized embryos and the targeting was verified by T7 endonuclease assay. The mutations were determined by sequencing. Collagen type I extracted from skin and bone was analysed by SDS-PAGE.
Results
Tmem38b is present in a single copy in the zebrafish genome and we demonstrated by qPCR and whole mount *in situ* hybridization that its expression is detectable very early during development in cranial bones and in the swim bladder. Two mutant lines were generated: one carrying an in-frame deletion of 24 nucleotides, that eliminates in TRIC-B the highly conserved KEV domain and the second with a deletion causing an out-of-frame transcript with a 90% of non-sense mediated decay. The α(I) bands of collagen type I showed a faster migration suggesting a lower level of post-translational modification. A preliminary characterization of the knock-out fish showed no difference in standard length during larval stage, but a reduction at 4 months post fertilization.
Conclusion
We successfully generated two tmem38b knock-out zebrafish that will allow to investigate the effect of TRIC-B in vivo during skeletogenesis and that may represent a powerful tool to understand the OI type XIV pathophysiology.
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Disclosure
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P38

Clinical features and approach to treatment in pediatric patients with McCune-Albright syndrome: monocentric experience

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McCune-Albright-Syndrome (MAS) is a rare multisystem disorder presenting with polyostotic fibrous dysplasia accompanied by a list of extraskeletal features including café-aulait spots and various endocrine hyperfunctioning. There is no effective treatment for FD in MAS nowadays. Patients with MAS ($n=60$, 49 girls(G) and 11 boys (B) have been diagnosed and followed up during 20 years in the Institute of Pediatric Endocrinology. First clinical manifestations were peripheral precocious puberty (PPP) in 77%, fibrous dysplasia (FD) in 18% and Cushing's syndrome (CS) in 5% of patients. PPP was seen as early as in 2 months-girl, fractures due to FD were seen since the age of 9 months, and CS was revealed in patients younger than 1-year. The way of treatment was determined for each patient according to the clinical signs. Girls with PPP with recurrent estrogen secreting ovary cysts were prescribed with antiestrogen treatment; long acting octreotide was given in case of growth hormone overproduction, methimazole was used for management of hyperthyroidism with 4 patients undergone thyroidectomy because of tissue overgrowth, oral phosphorus and calcitriol were given for management severe hypophosphatemia, adrenalectomy was the way of treatment for Cushing syndrome. Curettage and bone grafting was the most often used approach to the treatment of FD of low extremities. Unfortunately, surgery did not prevent recurrent fractures and progressive limb deformities in severe cases when the patients had total or subtotal FD involvement. Two girls underwent intramedullary nailing for treatment of femur fractures/In one case malposition occurred one year after the surgery and removal of the nail was performed. MAS can manifest in children at the age less than 1-year-old and involves the vast majority of tissues with different types of combinations of the features. Treatment of fibrous dysplasia is a challenging task with low efficacy, orthopedic surgery is controversial and requires more experience and further investigations.

Disclosure

The authors declared no competing interests.

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P39

Bone health outcomes in children with Duchenne Muscular Dystrophy

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Objectives

Deteriorating bone mineral density and fragility fractures are common complications of Duchenne Muscular Dystrophy (DMD). This study aims to evaluate the effects of bisphosphonate therapy and testosterone supplementation (for pubertal induction) on the bone health of children with DMD.

Methods

This retrospective cohort study examined the clinical records of children with DMD managed at the Neurogenetics and Endocrine clinics at The Children's Hospital at Westmead, NSW, Australia. A total of 50 boys were included in the study; 24 had received both corticosteroid and bisphosphonate treatment, of which 15 had also received testosterone for pubertal induction. 18 had received corticosteroid treatment only, 1 had received bisphosphonate therapy only, and 7 had received neither. The most common bisphosphonate regimen prescribed was intravenous zoledronate at a dose of 0.05 mg/kg six-monthly. Pubertal induction involved oral Andriol Testocaps (40 mg daily) increasing by 40 mg six-monthly to a maximum dose 160 mg daily. Primary outcome measures included bone mineral density (BMD) as measured by DXA in addition to fracture incidence.

Results

Total BMD z-scores (height-adjusted) were greater for children on bisphosphonate and corticosteroid therapy (median -0.319) compared to children who received corticosteroid treatment alone (median -1.323, $P=0.02$). Similarly, lumbar spine BMD z-scores improved from a median of -1.053 to 1.129 ($P<0.01$). There was no significant change in the incidence of fragility fractures pre and post bisphosphonate treatment. Pubertal induction did not increase BMD beyond that obtained from zoledronate alone.

Conclusion

Bisphosphonates play an important role in maintaining optimal bone mineral density in DMD. Larger studies are required to determine the best practice for pubertal induction in order to maximise bone accrual.

Disclosure

The authors declared no competing interests.

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P40

Stature and body weight more than age explain functionality level in children with Osteogenesis Imperfecta

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Objective

The purpose of this study was to verify the influence of age, body mass and stature on the functionality level of children with Osteogenesis Imperfecta (OI). METHODS: Thirty-eight children (8.21 ± 4.26 years, 19 girls and 52.6% OI type III) were evaluated during their hospitalization for Pamidronate intravenous infusion in the Brazilian Midwest reference hospital for OI treatment (University Hospital of Brasília). Body weight and stature were measured and capability and performance of functional activities were evaluated in three content domains: self-care, mobility and social function autonomy through the Pediatric Evaluation of Disability Inventory (PEDI). All data analyses were performed using SPSS program (SPSS Inc., USA). Two types of multivariate linear regression analysis - hierarchical and stepwise - were performed. The hierarchical method examined the weight of each variable accounting on PEDI score. To examine if a combination of predictors would explain more variance in the PEDI score, the variables entered in a multivariate stepwise analysis. The level of significance adopted was 0.05. RESULTS: The anthropometric values showed that 58.3 were classified as normal weight, 27.8% were overweight, 8.3% were obese and 5.6% presented severe obesity. The hierarchical regression results presented that height explained 66% of variance in the PEDI ($B=1.28$, SE $B=0.25$, $\beta=1.4$, $P=0.000$), and including weight in the second step the model explained 70% of the PEDI score ($B=-1.15$, SE $B=0.49$, $\beta=-0.63$, $P=0.026$). The age was not significant as a variable to explain PEDI when it was included in the model. Also, the stepwise regression retained only height and weight as predictive variables. CONCLUSION: Height and weight are more predictive variables of disability than age in children with Osteogenesis Imperfecta.

Disclosure

The authors declared no competing interests.

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P41

Increased prevalence of fractures in poorly chelated children with beta thalassemia

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Objectives

Patients with beta Thalassemia have been reported to have low bone mass; poorly chelated patients are likely to be at an even higher risk. Pubertal delay, hypogonadism, and reduced physical activity and sunlight exposure are likely to be additional contributors to poor bone health and increased fracture risk. The objective of our study was to assess the prevalence of fractures in Indian underprivileged, poorly chelated thalassaemic children.

Methods

We studied 167 children (3 to 18 years old, 72 girls) from June 2016 to March 2018. We assessed anthropometric variables, hemoglobin and serum ferritin concentrations. The children's fracture history was recorded. We performed posteroanterior spine imaging using GE iDXA (Wisconsin, MD, USA) and carried out vertebral fracture assessment using the adapted Genant *et al*. semiquantitative method (Genant *et al*. 2009).

Results
Mean age was 11.6±3.9 years. The mean height, weight, and BMI for age Z-scores were −1.9±1.2, −1.6±0.9 and −0.8±0.9, respectively. The mean Hb and serum ferritin concentrations were 8.1±1.7 g/dl and 2151.3± 1894.9 ng/ml respectively. In all, 25% of children had a history of low trauma fractures. Thirty-eight of the 167 children (23%) had a history of long bone fractures (LBFs); 7 children had 2 LBFs and 1 child had 3 LBFs. Three of these 38 children had vertebral fractures (VFs) in addition to LBFs; 2 children each had 1 VF, and 1 child had 2 VFs. Three of the 167 children (2%) had VFs without LBFs; 2 children had 3VFs and 1 child had 2 VFs.
Conclusion
The prevalence of fractures was high (25%) in thalassaemic children with poor chelation therapy in comparison to a prevalence of 9% reported in school going (2 to 18-year-old) Indian children (Khadilkar *et al*. 2015).
Disclosure
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P42

FGF 23 measurements in children with fibrous dysplasia: useful or not?
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Fibrous dysplasia is a mosaic disease resulting from post-zygotic activating mutations of the GNAS locus which codes for the α subunit of the Gs G-coupled protein receptor. In bone, impaired signalling results in impaired differentiation and proliferation of bone marrow stromal cells which are replaced by fibrous tissue resulting in bone fragility and dysplasia. All children diagnosed with Fibrous Dysplasia at The Royal National Orthopaedic Hospital since 2009 (103 children), excluding those with craniofacial involvement, were identified and prospectively screened for co-morbidities of the disease. Screening included clinical assessment, Whole Body MRI (WB MRI), measurement of blood and urinary phosphate levels, serum alkaline phosphatase calcium and FGF 23 levels. We correlated the levels of FGF23 with: serum and urinary phosphate levels; serum alkaline phosphatase levels; number of disease sites ie polyostotic vs monostotic; number of fractures: significant pain; and the need for surgical intervention.
Results
56/57 patients tested had elevated levels of FGF 23, the highest values were in the 4 patients clinically identified with phosphate wasting rickets, prior to screening. 2 other patients had levels >200 (normal range 0–100) but were asymptomatic. 4/93 patients had frank hypophosphateamia with increased urinary phosphate. 24/92 patients had elevated alkaline phophatase levels, without significantly higher levels of FGF23. 89/91 patients had normal serum calcium. Approximately one third of patients thought to have monostotic disease had polyostotic disease on WB MRI, levels of FGF23 did not predict this finding. 23/102 patients sustained fractures, almost all prior to diagnosis. The levels of FGF 23 taken at the time of screening ie not at the time of fracture, were not different from patients without a history of fractures. Patients reporting significant pain at the time of clinical assessment did not have significantly elevated levels of FGF 23.
Conclusion
FGF 23 levels were elevated in all but one patient in the cohort. The highest values were found in those with phosphate wasting rickets. However the level of FGF 23 was not useful in predicting any other clinical outcome and could not be used to predict disease progress. Serum phosphate remained the most useful test.
Disclosure
The authors declared no competing interests.
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P43

Bone health is compromised in adult patients with childhood-onset autoimmune-polyendocrinopathy-candiadis-ectodermal dystrophy (APECED)
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Objectives
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is an autosomal-recessive disorder caused by mutations in the autoimmune regulator gene resulting in insufficient suppression of autoimmunity. The impact of immunological abnormalities and the resulting endocrinopathies on bone health is largely unknown. We performed a comprehensive evaluation of skeletal parameters in a large cohort of adult patients with APECED.
Methods
All Finnish patients with APECED were invited to the study. Age- and gender-matched control subjects were selected through population register. Spinal radiographs were assessed for vertebral fractures. Volumetric bone mineral density (vBMD) and geometry in the total, trabecular and cortical bone compartments were measured with peripheral quantitative computed tomography (pQCT, XCT-2000) from the radius and tibia.
Results
Altogether 38 patients (22 females; median age 44.0 years, range 19.3–70.1 years) were examined. The patients were shorter (median height SDS (range), −1.3 (−2.9 −+1.4) vs −0.2 (−2.4±2.1), $P<0.001$) and had lower BMI (22.3 (15.0–40.7) vs 25.2 (18.8–43.9) kg/m^2, $P=0.001$) than the controls. Hypoparathyroidism (median age 6.5 years) and adrenocortical insufficiency (median age 11.0 years) had manifested in >80% of the patients. Ovarian insufficiency had been diagnosed between 12.6 to 36.5 years in 77% of females. Altogether 22 patients (58%) had a positive fracture history (1–5 fractures; median 1 fracture) and seven of them had experienced low energy fractures. Patients had on average experienced more fractures (1.2 per person) than the controls (0.7 per person, $P=0.039$). Three patients had vertebral fractures (7%). pQCT values at the radius (4 and 66% sites) for bone area, vBMD, or strength strain index *Z*-scores did not differ between patients and controls. In contrast, at the tibial sites (4 and 38%), patients had significantly lower trabecular vBMD (mg/cm^3, 216 (134–323) vs 235 (161–369), $P=0.028$) and lower cortical thickness (mm, 4.95 (3.37–5.86) vs 5.46 (2.76–7.32), $P<0.001$) than the control subjects. Total bone area did not differ between the groups.
Conclusion
Childhood-onset APECED with multiple risk factors constitutes a significant risk for bone health, associates with increased fracture risk and warrants careful follow-up of the patients already during childhood.
Disclosure
The authors declared no competing interests.
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P44

Bone mass and vertebral fractures in South African (SA) children on prolonged oral glucocorticoids (GCs) for chronic non-malignant illnesses
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Objectives
To assess lumbar spine (LS) BMD *Z*-scores and the prevalence of vertebral fractures using DXA lateral vertebral (VFA) assessment in children and adolescents with chronic illnesses on GCs.
Methods
All children between the ages of 5 and 17 years with chronic non-malignant illnesses who were on GCs (intravenous or oral) for greater than 3 months duration were evaluated. Study participants were children attending the paediatric sub-specialty clinics at Chris Hani Baragwanath Academic hospital between 21 January 2016 and 17 January 2019. Information on the primary diagnosis, anthropometric measurements and medications prescribed and their dosages were recorded at time of evaluation. DXA scans of lumbar spine (LS) and lateral vertebral fracture (VFA) assessment were performed using a Hologic Discovery (Software version Apex 4.0.2) with its white male and female reference values. Calcium, phosphate, alkaline phosphatase (ALP) and serum 25-hydroxyvitamin D (25(OH)D) were measured.

Results
Sixty-four patients (45% with renal, 23% with rheumatic, 16% with neurological, 13% with hepatic and 3% with respiratory conditions; mean age 11.5 ± 3.3 years, 56% boys, 92% SA black) were enrolled following informed consent from a guardian. The median duration of steroid treatment was 29.3 (IQR 14.6–46) months with a minimum duration of 3.7 months. Mean LS BMD *Z*-score was −1.66 ± 1.1. Forty-one percent of patients had a LS BMD *Z*-score ≤ −2. The prevalence of vertebral fractures on VFA was 17% (11 of 64 patients) of whom 5/11 had a LS BMD *Z*-score ≤ −2. Median serum calcium, phosphate, PTH and ALP were normal. Majority of patients (34/38) had 25(OH)D levels > 30 nmol/l and, one of the four patients with vitamin D deficiency had a LS BMD *Z*-score ≤ −2. No patients with vitamin D deficiency had vertebral fractures.
Conclusion
Despite the lower prevalence of fractures in healthy black children compared to white children in South Africa, the prevalence of vertebral fractures in predominantly SA black children on GCs with chronic non-malignant illnesses is high (17%) suggesting that routine yearly DXA scans including VFA is warranted in this highly at risk population.
Disclosure
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P45

Osteogenesis imperfecta type 15 with neurological phenotype associated with homozygous WNT1 mutation and uniparental isodisomy for chromosome 12

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Background
Osteogenesis imperfecta (OI) type 15 is a rare autosomal recessive form caused by WNT1 mutations. In addition to bone fragility it may be associated with neurological impairment. We report a unique case of OI type 15 in a child with uniparental isodisomy for chromosome 12 who also has von Willebrand disease type 2N, congenital ptosis, early onset scoliosis and a movement disorder.
Presenting Problem
A female infant was delivered normally at 42 weeks' gestation to healthy, unrelated parents following unremarkable antenatal scans. On day two she was not moving her right arm and right humeral and incidental right prenatal clavicle fractures were identified. Skeletal survey at 12 weeks revealed multiple healing rib and long bone fractures, multi-level vertebral compression fractures and left convexity thoracic scoliosis; no Wormian bones. Aged four months she had white sclerae, congenital left ptosis, no hypermobility, and abnormal extensor posturing of neck and trunk. CGH microarray revealed uniparental isodisomy for chromosome 12. OI genetic testing identified a homozygous novel pathogenic duplication c.216dup in exon 2 of WNT1 on chromosome 12, predicted to cause a truncated protein. Father is heterozygous. In addition, von Willebrand disease type 2N was identified, with homozygous c.2561G > A substitution in exon 20 of VWF, also on chromosome 12. Neuroimaging was normal.
Clinical management
Aged 12 months she started pamidronate. Latest spine x-ray aged 22 months revealed improved modelling at most vertebral levels, despite ongoing long bone fractures. Her movement disorder has evolved, with orolingual dyskinesia triggered by pain and excitement causing recurrent lip and tongue biting, and involuntary limb posturing apparent on activity. Her scoliosis is stable and managed with specialist seating and an OI Lycra suit.
Discussion
The precise mechanism linking WNT1 mutations with OI is not fully understood, however the Wnt signalling pathway is one of the key regulators of bone homeostasis and osteoblast activity. The role of bisphosphonates in this setting is less clear, however this child has responded positively. The neurological phenotypic spectrum associated with WNT1 is also not yet fully characterised. Further study is required to determine optimum therapeutic options and achieve best possible quality of life.
Disclosure
The authors declared no competing interests.
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P46

Vertebral fractures are more prevalent than long bone fractures in boys with glucocorticoid-treated Duchenne Muscular Dystrophy: Results of a prospective observational study

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Objectives
Osteoporosis is a frequent cause of morbidity in boys with glucocorticoid (GC)-treated Duchenne Muscular Dystrophy (DMD). We sought to determine the frequency and characteristics of the two most debilitating types of fractures, vertebral and long bone (VF and LBF), in pediatric DMD.
Methods
This was a prospective, bi-centre, single-visit observational study in boys 4 to 17 years of age with genetically-confirmed DMD. The bone health assessment included radiologically-confirmed low-trauma LBF, a lateral spine radiograph for VF assessment (T4 to L4) according to the Genant method (triple read by pediatric radiologists), anthropometry, pubertal staging, nutritional assessment, muscle function testing, and serum bone metabolism markers.
Results
Sixty boys with DMD were enrolled (mean age 11.5 ± 3.9 years); 56/60 were GC-treated. Eighteen boys (30%), all GC-treated, had a total of 59 VF (64% of VF were mild, 27% moderate, 9% severe); 13/18 boys had mild VF as the worst grade (72%), 4 moderate and 1 severe. Twenty-three % of VF were at T6 and T7, and the median number of VF per patient was 2.0 (range 1 to 14). Forty-one % of boys with any VF were asymptomatic, including 3/5 boys with moderate/severe VF. There were 12 LBF in 10/60 boys (17%, all GC-treated). The most frequent sites of LBF were the humerus (50%), followed by the radius (17%), tibia (17%) and femur (16%). 3 boys had both VF and LBF. There were no significant differences in anthropometry, pubertal stage, calcium and vitamin D intake, and muscle function testing between boys with and without fractures (all, $P > 0.08$). However, boys with VF, but not with LBF, had lower P1NP (111 ± 62 vs 221 ± 156 ng/ml, $P = 0.002$) and CTX (0.25 ± 0.23 vs 0.47 ± 0.35 ng/ml, $P = 0.02$).
Conclusions
In this cohort, VF were more frequent in boys with GC-treated DMD than LBFs; upper and lower extremity LBF occurred with equal frequency. Most boys with VF were asymptomatic; therefore, VF would have gone undetected in the absence of a spine radiograph (including in 60% of boys with moderate/severe VF). Low bone turnover may be a clinical marker of VF in this setting.
Disclosure
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P47

Anorexia nervosa: weighing in on bone health surveillance: When should it be performed?

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NICE guidelines (UK) recommend that bone mineral density (BMD) scans, corrected for bone size (bone mineral apparent density [BMAD]) should be performed for patients with anorexia nervosa (AN) when underweight for a year or more. The number of patients identified with low bone mineral density or vertebral fractures remains low in this population. However, referrals for dual-energy X-ray absorptiometry (DXA), vertebral fracture assessment (VFA) and peripheral quantitative computed tomography (pQCT) have increased significantly, over the last few years.

Method

We retrospectively reviewed AN patients referred for scanning over a 5 year period to observe the number identified with low BMD as per the ISCD 2013 guidelines. Vertebral and long-bone fractures were also recorded by interrogating our local imaging archive system. Demographic data, bone health history and baseline BMD parameters was collated.

Results

Sixty-two (62) patients were identified (58 female and 4 male). Eight patients had a BMAD *Z*-score < -2.0 however only one had evidence of a mild vertebral fracture with no long-bone fractures reported. One patient had a Total Body Less Head (TBLH) *Z*-score < 2.0 but with no evidence of vertebral or long bone fractures. Four patients had pQCT total, trabecular and cortical content *Z*-score <2.0 with no evidence of vertebral fracture and one reported long bone fracture. However, thirty-nine patients had muscle area for height *Z*-scores <2.0. Of five patients with vertebral fractures, four had reduced muscle area. Similarly, of twelve patients with long-bone fractures, six had reduced muscle area.

Conclusion

Our findings confirm that incidence of decreased BMD and vertebral fractures in adolescents with anorexia nervosa is low. Low muscle mass rather than bone density is a better predictor of fractures. Therefore body mass index criteria should be incorporated into the referral criteria for bone health surveillance in AN patients rather than duration of anorexia alone.

https://www.nice.org.uk/guidance/ng69/evidence-Accessed 08/02/2019

Disclosure

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P48

Does improved genetic screening make it more difficult to diagnose Osteogenesis Imperfecta?

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Background

Genetic advances have led to the identification of 14 genes implicated in Osteogenesis imperfecta [OI], encompassing 96–98% of cases. Hallmark features of osteogenesis imperfecta include fractures from minimal trauma, bowing of the legs and growth retardation. Non-skeletal features include blue sclera, dentinogenesis imperfecta, hearing and refractory visual deficits, pulmonary dysfunction and cardiac valvular malformations. Classical radiographic features are that of generalized osteopenia, fractures and wormian skull bones.

Presenting Problem

The proband is the second child of non-consanguineous parents, referred to our service at 10 months with a history of multiple fractures from minimal trauma. She was delivered by LSCS for low-lying placenta and breech presentation at term. Birth weight was 1.95 kg. Fractures were noted from Day 3 of life affecting other femurs and tibiae. A skeletal survey was carried out at 5 months and confirmed multiple wormian skull bones, flattened thoracic vertebrae and bilateral coxa valga. In addition, she has required an atrial septal defect repair and ongoing feed-aspiration. Hearing and vision are normal, with dental review pending. She has marked global development delay and is unable to sit unsupported at 15 months and unable to grab objects. The family history is negative for fractures or early osteoporosis but there is strong history of multiple miscarriages of unknown cause.

Clinical management

She is receiving ongoing multidisciplinary management including endocrinology, general paediatrics, specialist physiotherapy, dental and ophthalmology review. Extended genetic panel for collagen gene analysis has not yielded a pathogenic mutation and microarray is normal. No active medical treatment has been initiated as she has not incurred any further fracture since referral. Recent MRI brain scan has shown polymicrogyria of unknown origin which would explain her profound developmental delay.

Discussion

Although next generation sequencing has identified the majority of genes implicated in the pathogenesis of early primary osteoporosis, there remain a small number of unsolved cases. This proband meets the clinical criteria for a diagnosis of osteogenesis imperfecta and would have been expected to display an abnormality in collagen gene sequencing but she has eluded genetic diagnosis. To date there are no published links between polymicrogyria and osteogenesis imperfecta.

Disclosure

The authors declared no competing interests.

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P49

Bone mineral density and vitamin D status in children with chronic neurological syndromes - clinical observations

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Background

Some of the risk factors for osteoporosis population include: chronic immobilisation, insufficient dietary supply of calcium and vitamin D, decreased physical activity and long-term pharmacological treatment (glucocorticoids, anticonvulsant drugs). In disabled children and adolescents, the negative impact of these factors may cumulate to considerably impair the quality of life.

Objectives

The aim of our study was to assess the vitamin D status and bone mineral density in children with chronic neurological syndromes.

Material and Methods

A total of 34 children between 3 and 18 years of age were examined: 9 children with muscular dystrophy, 17 with cerebral palsy and 8 with lumbar myelomeningocoele. All the subjects underwent the following assessments: measurement of the concentration of the hepatic metabolite of vitamin D and total body less head and/or lumbar spine densitometry by dual energy X-ray absorptiometry (DEXA). Low bone mass or low bone mineral density were diagnosed if the *Z*-score value was found to be equal to or below –2.0.

Results

Indications for the above tests were chronic immobilisation or motor activity restriction, and - in 10/34 children - femoral or vertebral fracture. Vitamin D deficiency (<30 ng/ml) was detected in 27/33 patients ($>81\%$). Low bone mass on densitometry was demonstrated in 27/34 and osteoporosis in 10/34 subjects (*Z*-score $\leq$ –2.0).

Conclusion

Bone densitometry should be included in the standard of care for children with chronic neurological syndromes, and early detection of low bone mass should be an indication for treatment with calcium and vitamin D.

Disclosure

The authors declared no competing interests.

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P50

Treatment with asfotase alfa for patients with infantile hypophosphatasia and screening plan of hypophosphatasia by low ALP level and dental findings in Korea

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Background

Hypophosphatasia (HPP) is a rare skeletal disease characterized by defective bone and teeth mineralization and the deficiency of tissue non-specific alkaline phosphatase activity. This disorder is caused by mutations in the ALPL gene, which encodes TNAP. The clinical presentation of HPP varies greatly, ranging from stillbirth without bone mineralization (perinatal form) to findings in later

life, such as delayed walking, short stature, skeletal deformities, bone pain, and pathologic fractures (childhood and adult form).
Presenting Problem
HPP should be considered when serum ALP is continuously low. The diagnosis is based on clinical examination, radiologic findings, biochemical parameters of reduced ALP activity, elevated serum and urine levels of TNAP substrates, and molecular analysis of the ALPL gene. The prognosis for the infantile form is poor, with approximately 50% of patients dying within the first year of life from respiratory failure. Asfotase alfa, a bone-targeted, recombinant TNAP, has recently been developed to treat HPP complications.
Clinical management
We describe the clinical features, biochemical findings, molecular analysis, and first clinical experience of treatment with asfotase alfa in patients with infantile HPP in Korea. Patients received asfotase alfa with dose of 2 mg/kg three times weekly subcutaneously. All patients survived and the radiographic findings, laboratory findings, developmental milestones and respiratory function were improved. Injection site reactions were the most frequent adverse events, however, no serious adverse events were noted. Our results add support to the safety and efficacy of treatment with asfotase alfa for HPP patients.
Discussion
Accurate diagnosis and prompt treatment play an important role for avoiding preventable morbidity and premature mortality in patients with HPP. A persistently low ALP level in patients with unspecified diagnoses could be a key to diagnose HPP. Premature exfoliation of primary teeth may be the first manifestation of HPP and the general dental practitioner plays an important role in recognizing dental anomalies and referring patients at an appropriate time. Our screening of HPP planned by age/sex-specific reference ranges of ALP and collaborative work with dental doctors could prompt physicians to investigate for undiagnosed HPP. This is imperative to ensuring early diagnosis and good quality patient care.
Disclosure
The authors declared no competing interests.
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P51

Higher dose of burosumab is needed for treatment of children with severe forms of X-linked hypophosphatemia

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Background and aim
Burosumab is a monoclonal antibody against anti-FGF23, which has been recently approved for treatment of X-linked hypophosphatemia (XLH). Beyond clinical trials, little is known about its efficacy/safety in clinical practice which is the aim of study.
Patients/Methods
39 children with XLH were switched from conventional therapy to burosumab (starting dose 0.4 mg/kg), because of following indications: non-responder to conventional therapy (persistence of leg deformities, elevated alkaline phosphatase, need for orthopaedic surgery, presence of neurological, dental, hearing complications, secondary hyperparathyroidism, height < -2SDS); intolerance to conventional therapy (nephrocalcinosis, hypercalciuria) or late diagnosis (>8 years). Serum phosphate level (sP) was checked before starting burosumab (M0) and monitored every 2 weeks for dose adjustment (target sP >1.2 mmol/l). Other parameters (weight, height, ALP, 1,25(OH)2D, PTH, TmP/eGFR, CaU/CrU, side effects) were checked at M0, thereafter at 3 and 6 months of treatment (M3-M6).
Results
25 girls/14 boys (mean age of 9.6 ± 3.8 years; 84.6% of subjects ($n=33$) presented complications) were treated with conventional therapy for 7.7 ± 3.8 years before starting burosumab. 26 patients completed 6 months of treatment. Upon burosumab, levels of sP, TmP/eGFR, 1,25(OH)2D increased significantly (sP $=0.7\pm1.1$ - 1.2 ± 0.2 - 1.1 ± 0.1 mmol/l; TmP/eGFR $=0.6\pm1.1$ - 1.1 ± 0.2 - 1.0 ± 0.2; 1,25(OH)2D $=26.0\pm15.3$ - 73.4 ± 24.0 - 88.0 ± 34.4 pg/ml at M0-M3-M6, respectively, p for trend $=0.000$) and ALP decreased (413 ± 163 - 333 ± 150 UI/l at M0-M6, respectively, $P=0.3$). However, PTH and CaU/CrU were not modified during the treatment. At M6, average dose of burosumab was 1.3 ± 0.5 mg/kg (45 ± 23 mg); 61.5% ($n=16$) of patients did not achieve target sP level. At M6, 27% ($n=7$) of subjects received the maximal dose of burosumab (2.0 mg/kg or 90 mg), yet had low sP level. The number of complications was positively associated with the final dose of burosumab (32 ± 13 vs 31 ± 16 vs 57 ± 24 mg for children with 0, ≤2 and >2 complications, respectively, p for trend $=0.004$). We did not observe severe adverse events during the treatment, the most frequent side effect being redness at sites of injection.
Conclusion
Treatment with burosumab restores phosphate reabsorption, increases sP and endogenous 1,25(OH)2D synthesis. The dose of burosumab needs to be increased with the severity of the disease.
Disclosure
The authors declared no competing interests.
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P52

Variable familial expression of spondylometaphyseal dysplasia with coxa vara and a novel FN1 mutation

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Background
Spondylometaphyseal dysplasias (SMDs) comprise a diverse group of skeletal dysplasias and often manifest as short stature, growth-plate irregularities, and vertebral anomalies. One such condition is SMD with 'corner fractures' (OMIM #184255). These individuals generally show development of coxa vara, scoliosis and triangular ossification centers at the edges of metaphyses that simulate fractures.
Presenting problem
To date only 16 patients with SMD and biallelic fibronectin (FN1) mutations have been reported. The majority had a substitution of a cysteine in the N-terminal assembly region. We report a family with a novel missense mutation.
Methods
Analysis of candidate genes by massive parallel sequencing (TruSightTM One Panel, NextSeq Illumina) and data analysis by SeqNext (JSI).
Clinical Management
The novel missense mutation in FN1:c.341G $>$ C (p.Arg114Pro) was inherited from the mother. The girl, born at term BW 1.895 kg (-3, 03 s.d.), L 44 cm (-2,83 s.d.), was first evaluated for short stature and developing waddeling gait at 7 years. Radiographic features were compatible with a bilateral 'perthes like' hip dysplasia, coxa vara, shortened femoral neck, flattened epiphysis with corner fractures, abnormal vertebrae with end-plate irregularities. Height was113,5 cm (-3,5 s.d.) at 8.4 years. The brother was born preterm at 33/3 weeks with normal birth measurements, normal development. At 9 years he developed an abnormal gait caused by unilateral coxa vara. Height was 127.6 cm (P10). The mother was evaluated in her childhood with short stature and coxa vara. Final height was 149 cm. In adulthood she developed painful osteoarthritis and osteonecrosis affecting mainly knees and ankles.
Discussion
The report expands the clinical phenotype and demonstrates familial variability concerning onset and severity of symptoms.

Disclosure
The authors declared no competing interests.
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P53

Successful treatment with enzyme replacement therapy in a girl with severe infantile Hypophosphatasia

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Background
Infantile Hypophosphatasia (HPP) is an inborn error of metabolism characterized by low serum alkaline phosphatase activity caused by loss-of-function mutations within the ALPL-gene encoding the tissue nonspecific isoenzyme of ALP (TNSALP). TNSALP controls skeletal and dental mineralization by hydrolyzing inorganic pyrophosphate, a potent inhibitor of bone mineralization. Patients develop substantial skeletal disease, failure to thrive, and sometimes vitamin B6–dependent seizures before 6 months of age. Without treatment, HPP results in 50–100% mortality, typically from respiratory complications.
Presenting problem
We present a 3 months old girl with infantile HPP caused by 2 heterozygous mutations in the ALPL gene. At the age of six weeks she presented with a lack of weight gain because of vomiting and respiratory insufficiency. Clinical investigations showed rhizomelia of the upper arms and femora, short stature, broad nose bridge, high forehead, a bulged fontanelle and muscular hypotension. A single cerebral seizure terminated spontaneously. Laboratory examinations revealed a very low serum ALP activity and a high urinary excretion of phosphoethanolamine. Radiographic findings include hypomineralization with cup-shaped distensions of the metaphysis and irregular zones of ossification.
Clinical Management
Starting enzyme replacement treatment 2 mg/kg s.c. every other day was associated by a supportive therapy with oxygen, enteral nutrition through nasogastric tube, physiotherapy and supplementation of calcium, pyridoxine and analgetics. As a result of therapy x-rays showed an increase of bone mineralization. Stabilization of the chest wall led to a normal breathing pattern without need of oxygen support after 8 weeks. After improvement of vomiting tube-feeding could be weaned after 4 weeks with good weight gain. Muscular strength and neurological function improved also.
Discussion
Infantile hypophosphatasia is extremely rare and may be life threatening. Our case demonstrates that treatment with the recombinant enzyme therapy led to an improvement in muscular hypotonia, neurological problems and skeletal mineralization and therefore, respiratory function, growth and weight normalised.
Disclosure
The authors declared no competing interests.
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P54

Is oral health correlated with skeletal phenotype in primary metabolic bone diseases? A preliminary report of the Greek experience

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Introduction
Oral health problems are common in patients with primary metabolic bone diseases. We aimed to investigate the oral health of patients with primary osteoporosis and genetic mineralization disorders and correlate the oral health findings with clinical, imaging and laboratory parameters.
Patients and methods
Twenty nine patients 2.8y-17y (15 males, 22 prepubertal) with primary metabolic bone diseases underwent a comprehensive dental examination. Dental caries, oral hygiene, severity and degree of periodontal diseases, developmental disturbances of the dental tissues and orthodontic problems were correlated with their dietary calcium intake, clinical status (growth, fracture history), bone densitometry and metabolic bone markers performed during the same period (procollagen type I C-propeptide, PICP and urinary deoxypyridinoline/creatinine, DPD/Cr).
Results
Twenty-two patients had primary osteoporosis (20 with osteogenesis imperfecta); 10 of them were on bisphosphonates. Seven patients suffered from mineralization disorders (MD, ie hypophosphatasia and genetic types of rickets). In the PO group, 45.5% had dental caries, 50% had developmental disturbances of the dental tissues and 31.8% had orthodontic problems, while the corresponding percentages for the MD group were 42.9%, 16.7% and 57.1%. Reassuringly, there was no case of jaw osteonecrosis amongst those on bisphosphonates (duration of treatment: 1.5y-9y). In both groups, the presence of dental caries in permanent teeth was significantly correlated with oral hygiene and dietary calcium, while in the PO was also correlated with DPD/Cr, a marker of bone resorption. Interestingly, for primary teeth in both groups, higher caries index was correlated short stature. Finally, developmental disturbances of the dental tissues significantly correlated with lumbar spine bone mineral density (LS BMD) and BMI Z-scores in the PO group only.
Conclusion
Prevention of poor dental health for paediatric patients with primary metabolic bone disorders is of paramount importance. Potentially, total calcium intake, LS BMD Z-scores and reduced height could be indicators of dental problems and might help prioritizing those patients more in need of a detailed and regular dental review. Further analysis is needed to clarify the above correlations and reveal cut-off points of those parameters that place patients at a high risk for dental problems.
Disclosure
The authors declared no competing interests.
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P55

Abstract withdrawn.

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P56

Unusual cause of abdominal pain in adolescent girl

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Background
Recurrent abdominal pain is common in children and adolescents. This symptom could be raised by the complex of both functional and organic etiologies.
Presenting problem
We put forward a seventeen-years-old adolescent girl with personal history of repeated abdominal pain and urinary tract infections. Her family history was negative.
Clinical management
Our patient was admitted to hospital due to recurrent abdominal pain and third manifestation of pyelonephritis (11/2017, 1/2018, 10/2018). Cultivation reported on a significant bacteriuria - E.coli 106. She suffered from right side backache at the time of admission. The ultrasound examination revealed the presence of 4 mm stone in the upper calyx of the right kidney. Metabolic investigation showed hypercalcemia, hypercalciuria, and inappropriately elevated serum parathyroid hormone level. Blood levels of other minerals as well as alkaline phosphatase activity were in normal range. Control renal ultrasound six weeks later detected hyperechoic deposit (13 mm) in cranial part of the right kidney and calculus (8 mm) in the upper calyx of the left kidney. Cervical ultrasonography described parathyroid glands with normal appearence. Parathyroid scintigraphy with MIBI scan by SPECT/CT revealed MIBI accumulation in the lover pole of the right thyroid gland lobe, persistent on the late scan. This finding corresponded to adenoma or parathyroid gland hyperplasia. Surgery was performed and suspected parathyroid gland was removed with significant intraoperative decrease of serum parathormone concentration (from 22.73 to 2.45 pmol/l). At follow-up examination two weeks later total plasma calcium, ionized calcium, and parathormone levels remained within normal range. Histopathological examination confirmed the diagnosis of parathyroid adenoma.

Discussion
Primary hyperparathyroidism is ranked among most common endocrine diseases, affecting predominantly postmenopausal women. In children and adolescents, urolithiasis and primary hyperparathyroidism is a rare condition. It is mostly caused by adenoma of parathyroid gland. The possibility of primary hyperparathyroidism should be included in the differential diagnosis in case of repeated pyelonephritis, abdominal pain and nephrolithiasis in a pediatric patient.
Disclosure
The authors declared no competing interests.
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P57

Effective therapy with growth hormone of an adolescent patient with growth hormone deficiency and osteopetrosis: A case report

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Background
Osteopetrosis (OP) is a bone disease which is characterized by increased bone density. Autosomal dominant osteopetrosis type II (ADO II, also called Albers-Schönberg disease) is the most common type and it is caused by heterozygous mutations in the chloride channel 7 (CLCN7) gene.
Presenting problem
To present a patient with known medical and family history of osteopetrosis, who was diagnosed with Growth Hormone (GH) deficiency and was treated with recombinant growth hormone (rGH), which resulted in acceleration of growth velocity and attainment of final height within normal range.
Clinical management
A 12 and 7/12 years old male adolescent was referred because of short stature and deceleration of growth rate. He was the product of an uneventful full-term pregnancy with BW 3350 g and BL 52 cm. The patient was diagnosed in Canada with autosomal dominant osteopetrosis type II. There was also a positive family history of the disease for his father and his brother. As his height was- below the 3rd percentile (-2 S.D.) and IGF-I levels low, growth hormone (GH) stimulation tests were performed and GH deficiency was diagnosed on the basis of a glucagon and clonidine stimulated GH peak below 5 ng/ml. Magnetic Resonance Imaging (MRI) of the pituitary gland was normal. Treatment with rGH was initiated at a dose of 200 μg/kg with a prompt response of growth velocity acceleration (6.6 cm/year), faster than expected according to the growth rate predicting program (igrow). He continued therapy for five years, until he reached 17 and 9/12 years of age, when rGH treatment was discontinued. His final height was within the normal range for the age and sex, 169 centimeters (10th percentile). There were no complications during treatment or during follow up after discontinuation.
Discussion
To our knowledge this is the first report of a patient with osteopetrosis and GH deficiency treated with growth hormone. Growth hormone therapy can be beneficial for patients with GH deficiency and osteopetrosis. As osteopetrosis is a very rare condition further experience is needed.
Disclosure
The authors declared no competing interests.
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P58

The validity of serum alkaline phosphatase to identify nutritional rickets in Nigerian children on a calcium-deprived diet

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Objectives
Nutritional rickets results from the interaction of poor vitamin D status and limited calcium intake. Elevated serum alkaline phosphatase is a marker of impaired mineralization in many forms of rickets. We assessed the reliability of serum alkaline phosphatase in identifying nutritional rickets in calcium-deprived Nigerian children.
Methods
We reanalyzed data from a case-control study of Nigerian children with active rickets (cases) and age-, sex-, and weight-matched control subjects without rickets in an area where dietary calcium insufficiency is common (*J Pediatr* 2000;137:367–73). Children were classified as having radiographically active rickets prior to obtaining blood for biochemical analysis. We performed a multivariate logistic regression to assess the odds of rickets associated with varying alkaline phosphatase values, adjusting for age and sex.
Results
A total of 122 children with rickets and 121 control children had sufficient data ($n=243$) for analysis. Rachitic children had a mean ($\pm$S.D.) age of 54 ± 29 months, and 55 (45.1%) were male. Cases and controls had similarly low mean dietary calcium intakes (216 ± 87 and 214 ± 96 mg/day, respectively). Mean alkaline phosphatase values in cases and controls were 812 ± 415 and 245 ± 78 U/L, respectively ($P<0.001$). Serum alkaline phosphatase was negatively associated with serum 25-hydroxyvitamin D values ($r=-0.34$; $P<0.001$). In the model, the odds ratio (95% confidence interval) for rickets was 6.7 (4.1–12.2) for each 100 U/L increase in alkaline phosphatase. The area under the receiver operating characteristic (ROC) curve was 0.98, indicating a strong relationship between alkaline phosphatase and having rickets. Age and sex were not significant confounders ($P=0.71$). Test characteristics of alkaline phosphatase >350 U/L for identifying nutritional rickets in Nigerian children were: sensitivity 0.93, specificity 0.92, positive likelihood ratio 11.3, and negative likelihood ratio 0.07.
Conclusion
In Nigerian children with a low dietary calcium intake, an alkaline phosphatase >350 U/L effectively discriminated between children with and without nutritional rickets. Alkaline phosphatase is a low cost biochemical test that could be used to screen for nutritional rickets, but cut-point values require validation in other populations. Laboratory values for alkaline phosphatase need to be standardized for widespread population studies of nutritional rickets.
Disclosure
The authors declared no competing interests.
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P59

Effective treatment of a patient with Hypophosphatemic Rickets leading to normal adult height

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Background
Hypophosphatemic Rickets is an inherited disorder characterized by defect in bone mineralization, mainly in long bones due to hypophosphatemia. The most common form is the X-linked form but other forms such as autosomal dominant hypophosphatemic rickets and tumor-induces osteomalacia are also described. Symptoms usually begin in infancy or early childhood and there is a large spectrum of abnormalities. The most severe form causes bowing of legs, bone deformities, bone and joint pain, growth retardation and short stature.
Presenting problem and clinical management
To present the progress both biochemical and clinical of a boy with Hypophosphatemic Rickets from diagnosis till growth completion at 17 years of age. He was born at term with a birth weight of 3550 gm, length of 50 cms (25th-50thcentile) and head circumference of 35 cms. Growth failure was noted from the age of 28 months [Length: 85 cm (5thcentile), head circumference: 52 cm ($>$90thcentile), arm span: 84.5 cms, leg length: 31 cm, weight: 12.600 gm]. Baseline investigations including complete blood count, arterial blood gas, liver, renal and thyroid functions, 25 (OH) vitamin D and parathormone (PTH) were within reference range but serum phosphate was low ($P=2.5$ mg/dl) and alkaline phosphatase high (ALP$=522$ U/L). Clinically, he had bowed legs and X- rays revealed bone deformities. Therapy with phosphate per os and alfacalcidol was initiated and were instructed to increase dietary calcium. The boy was reevaluated every 6 months and dose was adjusted according to the levels of serum phosphate,

alkaline phosphatase and PTH. Growth velocity was also taken into consideration. Treatment goal was to keep alkaline phosphatase normal and phosphate levels above 3.2 mg/dl 2 hours postprandialy, avoiding secondary hypoparathyroidism. Although in early childhood genu valgum persisted, it was opted to proceed only with medical treatment. Bone deformity gradually improved and currently there is only minimal bowing. He entered puberty at the age of 12 yrs and today he has reached final height at 169.3 cms (25th centile) (target height: 178 ± 5 cm).
Discussion
Meticulous monitoring of growth velocity and biochemical markers and dose adjustment can assure normal growth and avoidance of secondary hypoparathyroidism and/or nephrocalcinosis.
Disclosure
The authors declared no competing interests.
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P60

FGF23-expressing osteocytes are confined to bone packets that completed primary mineralization in patients with chronic kidney disease on dialysis (CKD5D)

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Objectives
FGF23 is expressed in clusters of osteocytes at the trabecular periphery suggesting that FGF23-expressing osteocytes are confined to specific basic multicellular units (BMUs) at the trabecular surface. Higher numbers of FGF23-expressing osteocytes are found in chronic kidney disease (CKD) patients with preserved skeletal mineralization indices. We thus combined immunohistochemistry and quantitative backscattered electron imaging (qBEI) to explore the hypothesis that FGF23 expression is confined to BMUs that have successfully transitioned from primary to an early phase of secondary mineralization in CKD bone.
Methods
Histomorphometric analysis and immunohistochemistry for FGF23 expression were performed in un-decalcified bone from 4 patients (18–25 years) treated with maintenance dialysis (CKD5D). BE images were captured by scanning the entire cross-sectional area of the biopsy sample block with a resolution of 1.8 µm/pixel and mapped according to the FGF23 staining observed in the adjacent histological section. Mean calcium content was evaluated in selected bone packets and bone mineralization density distribution (BMDD) was assessed in trabecular and cortical compartments.
Results
Bone turnover was low in all patients although serum PTH levels were high in 3 probands. No osteomalacia was noted on histomorphometry. The average calcium concentration (CaMean) was within normal range or increased up to +7.4% in trabecular bone and up to +11.4% in the cortical compartment. Bone packets with high FGF23 expression were located at trabecular and osteonal surfaces, showed no features of active bone formation and were all mineralized above 18 weight% calcium. In the patient with low serum PTH concentrations, the peripheral matrix surrounding FGF23-expressing osteocytes was mineralized above 27 weight% calcium and the bone packets were higher mineralized than the adjacent older ones. In all other samples, the highest calcium contents were found in the oldest bone packets, deep within the bone matrix, which did not surround FGF23-expressing osteocytes.
Conclusion
This pilot analysis suggests that FGF23 expression in CKD5D bone is confined to osteocytes in rather young BMUs, at the trabecular periphery and on osteonal surfaces, that have completed primary mineralization. Further studies are ongoing to evaluate the relationship between bone turnover, bone material properties, and FGF23 expression in the context of CKD.
Disclosure
The authors declared no competing interests.
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P61

Biochemical and genetic analysis in patients with odontohypophosphatasia in Japan

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Background
Hypophosphatasia (HPP) is characterized by defective mineralization of bone and/or teeth in the presence of low serum alkaline phosphatase (ALP) activity and caused by mutations in the ALPL gene encoding tissue-nonspecific ALP. Odontohypophosphatasia (odonto HPP) is the mildest form of hypophosphatasia and characterized by dental complications without abnormalities of the skeleton system.
Objectives
We aimed to investigate biochemical and genetic features in patients with odonto HPP in Japan.
Methods
We analyzed 9 unrelated Japanese patients with odonto HPP who have visited to our hospital since 2008.
Results
The first primary tooth loss occurred at the age of 2.5 (1.3–4.0) years (median [min.–max.]). Seven patients were referred to our hospital from the department of pediatric dentistry, the nearest dental university hospital and two from the department of pediatrics, other hospitals. Height SDS and weight SDS at the first visit was 0.0 (−2.57 to +1.51) and 0.78 (−1.20 to +1.77), respectively. Serum ALP activities were decreased, 266 (192–361) U/L (The normal range at the age of 2 years is 410 to 1250 [male] or 1150 [female] U/L). Urinary phosphoethanolamine (PEA) levels were elevated, 604 (166–899) nmol/mgCr. In 4 patients, serum levels of pyridoxal 5'-phosphate (PLP) and pyridoxal (PL) were measured. PLP levels were high, 321.9 (132.6–647.2) nmol/L. PL levels were 32.7 (13.7–46.2) nmol/L. PLP/PL ratio was high, 10.2 (6.3–11.7). Ages at the first primary tooth loss were not associated with values of biochemical parameters. Serum ALP activities were negatively correlated with urinary PEA and serum PLP levels. Urinary PEA levels were positively correlated with PLP/PL ratio. Six patients had a heterozygous mutation in the ALPL gene; while only one patient had compound heterozygous mutations.
Discussions
Our study in Japan showed that odonto HPP, the mildest form of HPP, has the biochemical characteristics of HPP and that serum ALP activity is negatively correlated its substrate levels. Genetic analysis indicated the majority of odonto HPP is autosomal dominant form. Further studies, especially comparative analysis of odonto HPP with childhood HPP with premature teeth loss, will be needed to elucidate features of odonto HPP.
Disclosure
Alexion Pharmaceuticals.
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P62

Tissue non-specific alkaline phosphatase activity and mineralization capacity of bi-allelic mutations from severe perinatal and asymptomatic hypophosphatasia phenotypes: Results from an in-vitro mutagenesis model

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Introduction
Hypophosphatasia (HPP) characterized by reduced mineralization occurs from mutations in the tissue non-specific alkaline phosphatase (ALPL) gene. Individuals harbouring bi-allelic mutations are generally reported to be severely affected. We report the findings of *in vitro* functional studies following site-directed mutagenesis in bi-allelic mutations causing extreme clinical phenotypes; severe perinatal and asymptomatic HPP.

Objectives
Elucidate genotype-phenotype correlation using *in vitro* functional studies and 3 dimensional (3D) ALP modelling.
Methods
Clinical, biochemical and radiological features were recorded in two patients (P) with extreme HPP phenotypes: P1: perinatal HPP with compound heterozygous mutations (c.110T>C; c.532T>C); P2: asymptomatic with homozygous missense mutation (c.715G>T). P2's affected siblings (3 homozygous, 1 heterozygous) were also studied. Plasmids created for mutants 1 c.110T>C(L37P), 2 c.532T>C(Y178H) and 3 c.715G>T(D239Y) using *in vitro* mutagenesis were transfected into human osteosarcoma cells and compared to wildtype (WT) and mock cDNA. ALP activity was measured using enzyme kinetics with p-nitrophenylphosphate. Mineral deposition was evaluated photometrically with Alizarin Red S staining after culture with beta-glycerophosphate. Western blot analysis was performed to identify the mature type protein expression (80 kDa). Mutations were located on a 3D ALP model.
Results
Phenotype: P1 had extremely under-mineralized bones and pulmonary hypoplasia, typical of perinatal HPP. P2, diagnosed incidentally at 4 years, had normal growth and radiology similar to the siblings. All had typical biochemical features of HPP (low ALP, high serum pyridoxal-5'-phosphate) except heterozygous sibling (normal ALP). Functional assay: Mutants 1 and 2 demonstrated negligible ALP activity and mineralization (7.9% and 9.3% of WT, respectively). Mutant 3 demonstrated 50% ALP activity and 15.5% mineralization of WT. Western blot analysis detected mutants 1 and 2 as faint bands indicating reduced expression and mutant 3 as mature form protein (50% of WT expression). Mutant 1 was located near the Glycosylphosphatidylinositol anchor, 2 at the core structure and 3 at the periphery of the ALP protein structure.
Conclusion
Our findings expand the current knowledge of functional effect of individual mutations and the importance of their location in the ALP structure. Unlike the high intrafamilial variability reported with compound heterozygous mutations, homozygous mutations showed no variability enabling phenotype prediction in offsprings and genetic counselling.
Disclosure
Wolfang Högler has been an investigator in Alexion-sponsored clinical trials, is a board member of the global HPP registry and has received honoraria and consulting fees from Alexion.
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P63

Bone geometry and microarchitecture deficits in children with Alagille syndrome

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Objectives
Alagille syndrome (ALGS) is an autosomal dominant disorder attributed to mutations in the Notch signaling pathway. Children with ALGS are at increased risk for fragility fracture, but the etiology of this disposition is unknown. Our objective was to characterize bone mass, geometry, and microarchitecture in children with ALGS.
Methods
This was a cross-sectional study of 10 children (9 females) ages 8-18 years, with a clinical diagnosis of ALGS. Bone density was assessed via DXA. Tibia trabecular and cortical bone was assessed via pQCT (Stratec XCT 2000) at the distal 3% and 38% sites, respectively. Ultradistal tibia bone microarchitecture was assessed via HR-pQCT (Scanco XtremeCT II). Z-scores were calculated for DXA and pQCT measures. Reference data for the Xtreme CT II HR-pQCT scanner are not yet available, so these measures were descriptively compared to a sample of healthy children ages 5–20 years ($n=247$). Anthropometrics and labs were also collected.
Results
Based on one-sample t-tests, mean Z-scores for height and weight (both $P<0.05$), but not DXA bone measures, were negative and significantly different from zero. For pQCT bone measures, Z-scores for total bone mineral content (BMC) at the distal 3% site and cortical BMC, cortical area, and cortical thickness at the distal 38% site were negative and different from zero (all $P<0.05$). Compared to healthy children, those with ALGS generally had lower trabecular number, greater trabecular separation, and lower bone volume to total volume fraction despite having greater trabecular thickness (measured via HR-pQCT). Overall, bilirubin and bile acids, which are markers of hepatic cholestasis, were associated with poorer bone health. For example, bilirubin was associated with lower trabecular number (Spearman's rho$=-0.86$, $P=0.014$), greater trabecular separation (Spearman's rho$=0.82$, $P=0.023$), and greater cortical pore diameter (Spearman's rho$=0.99$, $P<0.001$) measured via HR-pQCT, and bile acids were associated with lower cortical area measured via pQCT (Spearman's rho$=-0.78$, $P=0.041$) and lower serum insulin-like growth factor 1 (Spearman's rho$=-0.86$, $P=0.002$).
Conclusions
Further investigation is needed to understand the factors contributing to ALGS-related cortical and trabecular bone inadequacies, and the manner in which these deficits contribute to increased fracture risk.
Disclosure
The authors declared no competing interests.

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P64

Missense mutations in ENPP1 result in osteoporosis in patients and is recapitulated in the ENPP1 loss of function murine model

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Biallelic ENPP1 deficiency in humans induces hypophosphatemic rickets in children characterized by increased circulating FGF23 levels and renal phosphate wasting ('Autosomal Recessive Hypophosphatemic Rickets Type 2', or ARHR2), but osteopenia or osteoporosis has not been described in adults. Here, we describe three adult male patients (ages 43, 59, and 62) suffering from early-onset osteoporosis who presented to the Institute of Osteology and Biomechanics at the University Hospital Hamburg, Germany. Two patients suffered from fractures in their thoracic spine and one a radial fracture. All patients exhibited elevated FGF23 levels and hypophosphatemia. DXA scans of hip demonstrated T-scores below −2.5 and HRpQCT demonstrated significantly reduced trabecular and cortical thickness of the tibia and radius. Next generation sequencing revealed that all 3 patients had heterozygous missense mutations in ENPP1: Y471C (1412A>G) (2 patients) and H777R (2330A>G) (1 patient). Enpp1asj/asj mice, a model of Enpp1 deficiency, were studied to understand the bone pathophysiology underlying this condition. Similar to what was observed in patients, 10 week-old male Enpp1asj/asj mice exhibited elevations in plasma FGF23 (350% of WT), hypophosphatemia (77% of WT), and osteopenia with reduced trabecular bone (trabecular BV/TV was 62% WT) and reduced cortical thickness (78% of WT). Other mineralization parameters in 10 week Enpp1asj/asj mice were as observed in ARHR2 – osteoid width was increased 130% of WT and mineralization lag time (MLT) was 214% of WT. Osteopenia progressed in 23 week-old male Enpp1asj/asj mice – BV/TV was 40% of WT, bone formation rate/bone surface area was 33% of WT, and mineral apposition rate (MAR) was 41% of WT. In conclusion, murine models of Enpp1 deficiency recapitulate the osteomalacia present in ARHR2 children and the osteoporosis present in adults with heterozygous ENPP1 mutations, and can therefore be used to model human bone mineralization disorders associated with ENPP1 deficiency. Our findings further suggest that parents of ARHR2 children may be at risk for early onset osteoporosis.
Disclosure
D.T.B. is an inventor of patents owned by Yale University, which describe therapeutics to treat ENPP1 deficiency. D.T.B is an equity holder and receives research and consulting support from Inozyme Pharma, Inc.

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P65

Tumor induced osteomalacia in a 12-year-old girl: Case report

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Background
Tumor Induced osteomalacia (TIO) is a rare acquired disorder in children characterized by hypophosphatemia, phosphaturia and rickets/osteomalacia. This condition is causes by mesenchymal tumor that produce phosphaturic factors resulting in decrease renal phosphate reabsorption. Here, we report a case of FGF-23 induced hypophosphatemic rickets due to a tumor of femoral bone in an adolescent girl.
Clinical case
The proposita is now 18 years old. She was first seen at age of 12 years with gradual onset of legs pain and muscle weakness for 2 years. Physical examination revealed short stature, rachitic rosary, bowed legs, epiphyseal enlargement of both wrists, knees and ankles. Radiography of wrists and knees showed fraying of metaphyseal region, physeal widening and generalize osteopenia. Investigations revealed BUN 8.1, Cr 0.3 mg/dl, Na 137, K 3.6, Cl 105, HCO3 25 mmol/l, Ca 9.4, P 1, Mg 1.8 mg/dl, ALP 1,704 U/L, iPTH 62 pg/ml, 25-OHD 29 ng/ml, 1,25 (OHD)2 12 pg/ml and tubular reabsorption of phosphate 79%. Because she had clinical features and laboratory findings consisted with hypophosphatemic rickets which occurred later in life, TIO was suspected. The plasma FGF-23 level was assessed and the result was high (690 RU/ml). The patients underwent various radiographic investigations, including TC99m MDP bone scan, octreotide bone scan and MRI whole body, but all fail to identify the location of tumor. She was treated with calcitriol and sodium phosphate supplement. However, she developed progressive muscle weakness, bowed legs, scoliosis and multiple fractures at lower extremities. At 6 years after initial presentation, whole body 68Ga-DOTATATE positron emission tomography (PET) with non-contrast CT demonstrated an ill-defined mixed osteolytic-sclerotic lesion, about 1 cm in diameter, at lateral part of left distal femoral shaft. Wide resection of the tumor was performed. After complete resection of tumor, her serum phosphate was normalized and radiographic signs of rickets were resolved.
Conclusion
TIO is an uncommon disorder in children but should be concern in case of hypophosphatemic rickets acquired beyond infancy period. The diagnosis is challenge because tumor is difficult to find by conventional radiological methods. Surgical removal of the tumor is the essential treatment.
Disclosure
The authors declared no competing interests.

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P66

Bone densitometry and body composition in children with hypophosphatasia

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Hypophosphatasia (HPP) is a rare genetic disease characterised by low tissue-nonspecific alkaline phosphatase activity, causing defective mineralisation of bone and teeth. There is limited data on the measurement of bone mineral density (BMD) and body composition in these children.
Objectives
To assess whether BMD and lean body mass (LBM) in treatment naïve children with HPP correlate with functional outcomes using the 6-minute walk test (6MWT).
Methods
A retrospective review of children ≥ 5 years with a diagnosis of HPP who underwent dual-energy x-ray absorptiometry (DXA) $\pm$ peripheral quantitative computed tomography (pQCT) of the radius at a tertiary paediatric centre was conducted. Bone mineral apparent density (BMAD), LBM and bone mineral content (BMC) were measured by DXA and volumetric BMD (vBMD) at distal radius (4% site) by pQCT.
Results
A total of 13 treatment naïve patients with HPP were identified (mean age 7.9 ± 2.8 years, 9 female), of whom 9 were childhood onset, 3 infantile and 1 odonto HPP. Mean z-scores for total body less head BMD and Lumbar Spine BMAD were within normal range (-0.9 ± 0.8 and -0.2 ± 1.3, respectively). The mean centiles for LBM for height and BMC for LBM (64 ± 29 and 38 ± 33, respectively) were also normal. Three children had mild ($<25\%$) vertebral height reductions in a maximum of 3 vertebrae. Seven HPP children had pQCT measured at distal radius with normal mean trabecular vBMD Z-score (-0.6 ± 1.0). Age, sex and height specific 6MWT centiles were determined in all 13 children with a substantially low mean z score of -2.48 ± 1.06. Mean 25 hydroxy vitamin D level at the time of DXA scan was 44.5 nmol/l.
Conclusion
Despite normal BMD, trabecular vBMD on bone imaging and LBM, our cohort of HPP patients demonstrated substantial reduction in functional exercise capacity. Proximal myopathy with microscopic muscle-fibre abnormalities has previously been reported in children with HPP which may explain the dissociation between bone imaging and functional outcomes.
Disclosure
The authors declared no competing interests.

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P67

Bone health outcomes in children and adolescents with neuromuscular disease

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Objectives
To compare and contrast the natural history of osteoporosis and response to zoledronate in children and adolescents with Duchene muscular dystrophy (DMD), spinal muscular atrophy (SMA) or other congenital muscular dystrophies (CMD).
Methods
A retrospective medical record review of fracture history, treatment and bone mineral densitometry of children managed at a tertiary centre in Sydney over the last 6 years.
Results
A total of 115 children/adolescents were included in this study. Diagnoses included DMD ($n=50$), SMA ($n=25$) or CMD ($n=40$). Mean age at first DXA was 8, 8.4 and 8.5 years, respectively. 86% of children with DMD were already on glucocorticoids at baseline DXA compared to $<5\%$ of those with SMA/CMD. All children were bisphosphonate naïve at baseline DXA. Children with SMA were significantly shorter than DMD/CMD but height-adjusted total body BMD (tBMD) was lowest in the DMD group (mean Z-score -0.5). Bone area was smallest in those with SMA (mean Z-score -3). Vertebral compression fractures were more evident in the DMD group. Serial DXAs were performed up to a mean age of 15 years. Over that timeframe, 25 (50%) with DMD were treated with zoledronate, 5 (20%) with SMA and 10 (25%) with CMD. Zoledronate did not significantly alter fracture rates but improved tBMD Z-scores by a mean of 0.5–1 and spine BMD Z-scores by a mean of 1–1.5 across the groups. In children not treated with bisphosphonates, there was a mean decline in tBMD and spine BMD Z-scores of 0.5–1.5, which was related to ability to stand rather than underlying neuromuscular condition.
Conclusion
Standing/weight-bearing remains a vital component in preserving tBMD but there are significant improvements in all groups with the use of bisphosphonates. Despite this, the ubiquitous use of glucocorticoids in DMD may be responsible for the increased vertebral compression fractures in this group. Further studies are required in order to determine the optimal treatment regimen in children and adolescents with neuromuscular disease and identify criteria for potential prophylactic bisphosphonate use.
Disclosure
The authors declared no competing interests.

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P68

Clinical case of a child with a hereditary vitamin D dependent rickets type 1a, complicated by rachitic lung and oxygen dependence

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Background
Hereditary pseudovitamin D-deficiency rickets, also known as vitamin D-dependent rickets type I, with an autosomal recessive inheritance, is caused by mutations in CYP27B1. It is characterized clinically by hypotonia, weakness, growth failure, and hypocalcemic seizures in early infancy. The patients also have hypocalcemia, radiologic findings typical of rickets, elevated serum parathyroid hormone concentrations, and generalized aminoaciduria. We present follow-up of a case with a novel mutation including improvement of disease monitored by computed tomography of the bones and lungs. Adequate treatment resulted in a normalized lung function.
Presenting problem
Our patient is the boy from consanguineous healthy caucasian parents. He was diagnosed with VDDR at age 3 years 8 months after he was admitted in Intensive Care Department (ICD) with respiratory insufficiency and started invasive lung ventilation. Earlier he was diagnosed with pulmonary hypertension and dilated cardiomyopathy. During examination growth failure and hypotonia were described. Diagnose was based on the hypocalcemia, hypophosphatemia, elevated serum parathyroid hormone concentration and radiological findings. During the genetic testing disease was confirmed. In CYP27B1 gene was founded a homozygous mutation NM_000785: exon1: c.C90A: p.Y30X that is not described in HGMD. Considering the exists of rickets, the boy was suspected having chronic lung disease.
Clinical management
A patient with chronic respiratory failure was treated with oxygen supplementation with therapy for underlying disease. We started treatment with active form of vitamin D and phosphate. The child was transferred to constant oxygen support at home. After 1 year of high dose active vitamin D treatment the patient is self-breathing without oxygen supplementation during all the day and night.
Discussion
The development of chronic lung disease in vitamin D-dependent rickets has combined reasons of both chest volume reduction and effect of the vitamin D on pulmonary cell biology and immunity with impact on inflammation. Despite the fact that respiratory manifestations were described earlier, in this case, important questions are needed about the timeliness of diagnosis, the risk of complications and treatment.
Disclosure
The authors declared no competing interests.

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P69

Experience of implementation and monitoring of burosumab treatment in a multi-disciplinary setting

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Objective
In 2018 we started treating children with X-linked hypophosphataemic rickets (XLH) with burosumab, initially as part of an industry-sponsored early access program. We present what we did, the barriers to implementation and broader lessons for the introduction of treatments for rare bone diseases in the future.
Method
Firstly, we identified suitable patients under the age of 18 years with XLH. For convenience we arranged dedicated clinics in which we were able to provide information and obtain consent efficiently. Within our institution, close liaison with and support from senior medical management and pharmacy were key elements that ensured we were able to proceed with the program in a timely fashion. Baseline assessment prior to first administration of the drug consisted of history and examination (including range of movement), fasted bloods, anthropometry, measurement of femoral and tibial torsion, plain radiographs of lower limbs, functional assessments (6 minute walk test (6MWT), ski sit, movement assessment battery for children) and quality of life assessment (PedsQL). Following commencement of burosumab, the same assessments were carried out 3 monthly in the same outpatient setting by the specialist team comprising a physician, clinical nurse specialist and physiotherapist.
Results
The response from patients regarding the clinics and the opportunity that they afforded for treatment was positive, colleagues in other centres provided indirect support and the data collected has provided useful regarding the impact of treatment on individuals and as part of a larger real-world cohort. However, the re-organisation of existing activity, increase in contacts and commitment to the collection and recording of more data was an increased burden of work. Practical and environmental difficulties risked failure of completion of data sets and threatened reliability e.g. availability of protected space to complete functional assessments such as the 6MWT.
Conclusion
The experience of implementing and monitoring burosumab has demonstrated the importance of working in a supportive and collaborative institutional and broader professional environment. However, if specialist teams are not properly resourced then there may be a risk that activity concerned with implementation of new drugs/technologies might occupy a disproportionate amount of time and/or be done without capturing key data.
Disclosure
Paul Arundel: Honoraria/expenses: Alexion and Kyowa Kirin. Expenses: BioMarin.

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P70

Metabolic bone disease of prematurity – comparing neonatal and endocrine approaches using a nationwide survey

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Objectives
Metabolic bone disease of prematurity (MBDP) is a multi-factorial condition characterised by a deficiency of calcium (Ca) and phosphate (PO4) mineral for incorporation into the organic bone matrix. Given the lack of clear guidelines, we conducted a survey across the United Kingdom of current practices, inviting both neonatologists and paediatric metabolic bone disease specialists (PMBS).
Methods
A web-based questionnaire survey was disseminated. Most questions required ticking of the options that applied, but a 5-point Likert scale was used to judge importance of screening and diagnostic tests (1 = not important, 5 = essential). Responses between neonatologists and PMBS were compared using appropriate statistical tests.
Results
Sixty nine neonatologists responded from 57 neonatal units (30% response rate) and 13 PMBS responded (68% response rate). In both cohorts, serum alkaline phosphatase (ALP) and PO4 were the most utilised investigations for screening and diagnosis. However, much greater emphasis was placed on plasma parathyroid hormone (PTH) in screening and in diagnosis by PMBS (average responses 4.1 and 4.2 respectively) than neonatologists (average responses 1.7 and 1.9 respectively) ($P < 0.0001$ for both screening and diagnosis). Also, greater emphasis was placed on radiograph appearances for diagnosis by MBDS than neonatologists (average response 3.6 vs 2.3 respectively, $P = 0.003$). Ninety-nine percent of neonatologists used PO4 supplements in treating MBDP, with 49% using alfacalcidol, and 28% using Ca supplements. Sixty-two percent of PMBS used PO4 supplements to treat MBDP ($P = 0.0003$), with 54% using Ca supplements and 23% using alfacalcidol. In both cohorts, monitoring of MBDP focussed on serum ALP, PO4 and Ca, but with PMBS more likely to utilise plasma PTH ($P < 0.0001$) and radiograph appearances ($P = 0.002$) also.
Conclusion
Neonatologists treat MBDP using PO4 supplements alone, relying on serum ALP and PO4 for screening and diagnosis. The use of PO4 supplements without consideration of Ca supplements to maintain physiological Ca to PO4 ratios will result in secondary hyperparathyroidism and skeletal demineralisation. Therefore measurement of plasma PTH is an important investigation for screening,

diagnosis and monitoring. Alfacalcidol has been introduced into routine practice, without rationale or evidence for benefit. Evidence-based consensus guidelines are needed to standardise safe practice.

Disclosure

The authors declared no competing interests.

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P71

Necessity of high dose and prolonged duration denosumab post stem cell transplant for TNFRSF11A osteoclast-poor autosomal recessive osteopetrosis

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Background

Hypercalcaemia is a risk following stem cell transplant (SCT) for all types of autosomal recessive osteopetrosis (ARO) due to restored osteoclast differentiation. This can be particularly severe in the osteoclast-poor (OP) form involving the tumour necrosis factor receptor superfamily 11A (TNFRSF11A) gene, encoding RANK. Denosumab, a monoclonal antibody blocking RANK activation, has been described for refractory post-SCT hypercalcaemia in two cases. Our case adds new information on dose, frequency and duration.

Presenting problem

A 2.3-year-old girl referred for investigation of short stature following craniosynostosis surgery. Investigation revealed underlying osteopetrosis due to TNFRSF11A gene compound heterozygous loss-of-function mutations (c. 414_427+7del and c.1664del). Maternal haploidentical SCT was undertaken aged 3.1 years. The anticipated hypercalcaemia following bone marrow engraftment developed on Day 18 (adjusted calcium 3.0 mmol/l RR 2.20–2.70) progressing despite a trial of hyper-hydration and diuretics.

Clinical management

Denosumab was initiated day 20 post-SCT (peak adjusted calcium 4.09 mmol/l): 0.13 mg/kg (1.2 mg; weight 9.2 kg) subcutaneously but achieved minimal improvement (4.09 to 3.65 mmol/l), so an additional larger denosumab dose (0.2 mg/kg) was administered 4 days later which normalised calcium (2.51 mmol/l). Recurrent, rapid onset, severe and symptomatic hypercalcaemia presented challenges to identify the ideal dosage regimen. Practical challenges included effective administration of small dose volume. Denosumab 0.25 mg/kg (2.4 mg) 4 weekly proved adequate, but larger doses (0.6 mg/kg) at 8 weekly intervals did not last longer and were associated with two emergency presentations with symptomatic hypercalcaemia at 7.5 and then 6.5 weeks post-dose. From 6–12 months post-SCT, denosumab 0.6 mg/kg 6 weekly has proven effective and is currently ongoing. Current status: otherwise good SCT function, markedly elevated bone mineral density (BMD) remains (L1–L4 BMD 1.052 g/cm^2, Z score +6.3) and two recent pathological fracture episodes (clavicle and proximal humerus).

Discussion

Hypercalcaemia post SCT for OP-ARO is an extremely rare but informative paradigm of osteoclast pathophysiology. The challenges in our case inform denosumab dose and duration in very young children for hypercalcemia post-SCT in osteopetrosis: effective regimen was denosumab 0.6 mg/kg (higher than previously reported, <0.3 mg/kg) 6 weekly ongoing 12 months post-SCT. We anticipate treatment duration of 18–24 months will be needed, and the ideal approach to treatment withdrawal under consideration.

Disclosure

The authors declared no competing interests.

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P72

Burosumab experience in UK X-linked hypophosphataemia children under five years old

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Objectives

X-linked hypophosphataemia (XLH) is a rare inherited form of osteomalacia characterised by low blood phosphate levels which lead to inadequate mineralisation of bone and rickets. Burosumab is an anti-FGF23 fully human monoclonal-antibody, and the first treatment to target the underlying pathophysiology of XLH. Real-world evidence is important in validating the findings of clinical studies. We report relevant real-world biochemical data on children under five years old for the first 6 months of burosumab treatment.

Methods

An early access program (EAP) for burosumab was made available for children in the United Kingdom with XLH in 12 specialist centres. Inclusion criteria for the EAP included radiographic evidence of disease, XLH confirmed by genetic PHEX mutation or familial X-linked inheritance of mutation or family history. Patients must have also had an unsatisfactory response to best available care and treatment. EAP enrolment was between January and March 2018. A total of 142 applications were received of which 135 were approved with 132 receiving treatment (dose in accordance with EMA marketing authorisation).

Results

Data are available on 10 children under five years (mean age 2.8 years; 1.6–4 years) who have completed a median of 6 months (20–26 weeks) of burosumab treatment. Mean dose administered by subcutaneous injection was 0.81 mg/kg (0.55–1.01 mg/kg) at week 0 and 1.09 mg/kg (0.57–2.01 mg/kg) at the end of the 20–26 week period. Mean fasting serum phosphorus was 0.73 mmol/l (0.6–0.83 mmol/l) in week 0 rising to 1.02 mmol/l (0.82–1.3 mmol/l) at week 20–26 representing a 40% increase in serum phosphate levels. Mean serum ALP fell from 808.2 IU/l (297–2124 IU/l) at week 0 to 612 IU/l (291–1459 IU/l) at week 20–26, representing a 24% decrease in ALP. No patients discontinued treatment due to adverse events.

Conclusions

Early data from treating young children with XLH with burosumab in a real-world UK setting demonstrate that key biochemical responses are aligned with findings from the clinical study program. This provides reassurance that the improvement in key biochemical parameters is consistent across all ages within its licensed indication.

Disclosure

The authors declared no competing interests.

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P73

Burosumab initiation in a UK X-linked hypophosphataemia cohort: real-world use resonates with research evidence

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Objectives
X-linked hypophosphataemia (XLH) is a rare inherited form of osteomalacia characterised by low blood phosphate levels which lead to inadequate mineralisation of bone resulting in rickets, skeletal abnormalities, physical impairment, weakness, and pain. Burosumab is an anti-FGF23 fully human monoclonal-antibody, and the first treatment to target the underlying pathophysiology of XLH. Real-world evidence is important in validating the findings of clinical studies. We report relevant real-world biochemical data following the first 6 months of burosumab treatment.
Methods
An early access program (EAP) for burosumab was made available for children in the UK with XLH in 12 specialist centres. Inclusion criteria for the EAP included radiographic evidence of disease, XLH confirmed by genetic PHEX mutation or familial X-linked inheritance of mutation or family history. Patients must have also had an unsatisfactory response to conventional treatment. EAP enrolment was between January and March 2018. 135 of 142 applications were approved. 132 have commenced treatment (dose in accordance with EMA marketing authorisation), of whom 31 have completed a median of 24 weeks (22–26 weeks) of burosumab treatment.
Results
Mean age enrolled was 7.2 years (range 1.6–14.7), 68% female and 32% male. Mean dose administered by subcutaneous injection was 0.51 mg/kg (0.28–0.95 mg/kg) at week 0 and 0.89 mg/kg (0.25–2.01 mg/kg) at week 24 (22–26 weeks). Mean fasting serum phosphorus was 0.73 mmol/l (0.5–0.91 mmol/l) in week 0 rising to 1.06 mmol/l (0.77–1.48 mmol/l) at week 24 (22–26 weeks) representing a 45% increase in serum phosphate. Mean serum ALP fell from 591.5 IU/l (261–4089 IU/l) at week 0 to 353.2 IU/l (190–733 IU/l) at week 24 (22–26 weeks), representing 40% decrease in ALP. No patients discontinued treatment due to adverse events.
Conclusions
Early data from treating children and young people with XLH with burosumab in a real-world UK setting demonstrate that key biochemical responses are aligned with the clinical research program findings. Ongoing monitoring and research is required to confirm the biochemical response translates to the expected subsequent impact on skeletal and non-skeletal outcomes, including linear growth and deformities.
Disclosure
The authors declared no competing interests.
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P74

Burosumab can improve pain and quality of life for children with X-linked hypophosphataemia and their families: a London centre's experience

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Objectives
Burosumab, a monoclonal antibody that therapeutically targets the underlying elevated levels of fibroblast growth factor 23 (FGF23) in X-linked hypophosphatemia (XLH), is now available to children out of trial conditions. Our objective was to describe the effect of burosumab on quality of life, functionality and pain in a clinical setting.
Methods
Questionnaire tools were completed at baseline, 6 and 9 months for 9 children with XLH starting burosumab at Evelina London Children's Hospital. Questionnaire tools used included: Core Paediatric Quality of Life Inventory (PedsQL Core), Paediatric Quality of Life multidimensional fatigue scale (PedsQL Fatigue), and Pain Severity Score (PSS) from the Brief Pain Index (BPI). 6-minute walk test (6MWT) and Movement ABC assessments were completed at baseline and 6 months to assess motor function and balance.
Results
Pain: There was an average increase in pain at 6 months which decreased to below baseline by 9 months. Mean PSS ($N=8$) was 2.13 (range 0–2.8) at baseline, 2.31 (range 0–6.75) at six months and 0.68 (range 0–2.25) at 9 months (maximum score 10). 2 patients reported no significant pain at baseline which remained unchanged. The increase of PSS at six months was only reported in 37.5% ($N=3$) patients. Fatigue: Patients felt less fatigued at 6 and 9 months compared to baseline, with Mean $\pm$ S.D. PEDsQL Fatigue scores improving from 62.9 ± 23.4 ($N=6$) to 74.1 ± 13.8 ($N=5$) at 6 months, and 72.2 ± 17.7 ($N=6$) at 9 months (maximum score 100).
Quality of life: Overall, quality of life improved with Mean $\pm$ S.D. PEDsQL Core total score improving from 66.1 ± 16.6 to 80.9 ± 15.1 at 9 months ($N=6$, maximum score 100). These scores and improvements were consistent across total, physical and psychosocial components. Function: All 4 patients evaluated had improvements in the 6MWT at 6 months, with Mean $\pm$ S.D. distance 258 + 87 metres at baseline and 402 ± 82 metres at 6 months. 3 out of 5 patients noted improvements in their Movement ABC score centiles.
Conclusion
These data shows that on standardised testing, Burosumab improves the pain, function, fatigue and overall quality of life over a 9-month period for children with XLH and their families in a clinical setting.
Disclosure
MS Cheung - Advisory Panel for Kyowa Kirin International.
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P75

Active vitamin D analogues and oral phosphate for the treatment of X-linked hypophosphataemia in paediatric patients: A systematic literature review and survey of expert opinion on current needs

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Objectives
X-linked hypophosphataemia (XLH) is a rare, inherited, genetic disease characterised by renal phosphate wasting, bone mineralisation defects, rickets, abnormal tooth development, poor growth and, often, bone pain. Common treatment of children involves supplementation with oral phosphate and active vitamin D (often termed 'conventional therapy'). The objective of this study was to identify and understand the perceived limitations of conventional therapy for the treatment of paediatric patients with XLH.
Methods
An insights protocol, comprising a systematic literature review on limitations of conventional therapy (1988–2018) alongside a two-round questionnaire gathering expert paediatric XLH physicians' opinions, was performed. The open-ended, first-round questionnaire prompted experts to list their perceived limitations of conventional therapy; responses were then coded into 'items' using thematic analysis. Experts were subsequently asked to rate their agreement with the inclusion of each item in the final study list (5-point Likert scale). Further ratings were also solicited on the frequency, impact on patients (5-point Likert), and challenge posed to treating physicians (10-point Likert) for each item.
Results
Following the literature review 72 full-text publications were identified, from which 16 items were coded. From the first-round questionnaire 18 items were coded; experts recommended all items for inclusion in the study in the second-round. In total, 23 distinct limitations of conventional therapy covering persistence, convenience and adherence; efficacy; and safety were identified, with 11/23 items identified in both the literature and assessment of paediatric expert opinion. Limitations relating to persistence, convenience and adherence consistently had the tightest agreement of scores across all second-round questions (average ranges: 1.67–4.67), compared with efficacy (2.0–5.2) and safety (1.71–6.29) limitations. When individual items were assessed, inability to normalise serum phosphate levels had the highest combined limitation score – combined frequency, patient impact, and treatment challenge scores – (14/20), followed by inadequate growth normalisation and nephrocalcinosis (13/20); the majority of the next five highest scoring items (12/20) related to adherence, persistence and convenience.
Conclusions
These results provide a better understanding of the limitations of conventional therapy, as well as the basis for a potential framework that could be used to assess new treatment options in the XLH treatment paradigm.

Disclosure
GA has received honoraria/consultancy fees and travel support from Kyowa Kirin Services Ltd. CdLC and ZM has received honoraria/consultancy fees from Kyowa Kirin Services Ltd. RJ is acting in a consultancy/advisory role for Kyowa Kirin Services Ltd.

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P76

Safety profile of asfotase alfa treatment of patients with hypophosphatasia: a pooled analysis

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Objectives
Asfotase alfa (AA), an enzyme replacement therapy, is the only approved treatment for pediatric-onset hypophosphatasia (HPP). We evaluated the safety profile of AA from the clinical trial program spanning pediatric and adult patients.
Methods
Safety data were pooled from 4 open-label, multicenter studies in children aged $\leq$3 years (study 002/003 [NCT00744042/NCT01205152]; $n=11$) and $\leq$5 years (study 010-10 [NCT01176266]; $n=69$) with HPP presenting before age 6 months; children aged 5–12 years with HPP (study 006/008 [NCT00952484/NCT01203826]; $n=13$); and adolescents/adults aged 13–65 years with HPP presenting at any age (study 009 [NCT01163149]; $n=19$). Safety events after the studies ended were not included.
Results
Overall, 112 patients (median [min, max] age at enrollment: 3.2 [0, 66.5] y; female: 51%) had a median (min, max) treatment duration of 2.7 years (1 d, 7.5 y) and average weekly total dose of 5.95 (2.1, 11.9) mg/kg. Adverse events (AEs) occurred in all patients; 26% of events were considered treatment-related; 74% were mild, and 21% were moderate. ISRs were the most common treatment-related AEs (73%). Ten (9%) patients experienced serious treatment-related AEs. Serious AEs of special interest were craniosynostosis (25%), injection-associated reactions (5%), injection site reactions (ISRs; 2%), ectopic calcifications (2%), and liver abnormalities/disease (2%). Ten infants with severe HPP (aged 1 d–20 mo at enrollment) died, four of pneumonia/sepsis and 1 each of respiratory failure and cerebral death, HPP-related complications, severe respiratory failure, cardiopulmonary arrest, severe cardiopulmonary insufficiency, and transtentorial and cerebellar tonsillar herniation from cerebral edema. Most deaths were considered related to underlying HPP. One death, attributed to pneumonia, was reported as possibly related to AA. AEs leading to withdrawal occurred in 11 (10%) patients; pneumonia and respiratory failure were reported in $\geq$2 patients. During treatment, 97/109 (89%) patients tested positive for anti-AA immunoglobulin G (IgG) antibodies, and 55 (57%) of these showed presence of neutralizing antibodies (NAbs). No relationship between patient anti-AA IgG/NAb status and treatment-emergent AEs was observed.
Conclusions
In this pooled analysis of mostly prepubescent children (84%) receiving AA for up to 7 years, ISRs were the most common treatment-related AEs.
Disclosure
MPW, NB, CH, WH, CRG, and PSK are clinical study investigators and have received honoraria, and/or institutional grant funding/research support, and/or speaker/consulting fees, and/or travel support from Alexion Pharmaceuticals, Inc. JH and VS are employees of, and may own stock/options, in Alexion Pharmaceuticals, Inc., which sponsored the study. SZ is an employee of Covance, Inc., and provided statistical services for this analysis under contract to Alexion Pharmaceuticals, Inc.

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P77

Long-term efficacy profile of asfotase alfa in the treatment of patients with hypophosphatasia: a pooled analysis

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Objectives
Asfotase alfa (AA), an enzyme replacement therapy, is the only approved medical treatment for pediatric-onset hypophosphatasia (HPP), which is caused by deficient tissue-nonspecific alkaline phosphatase activity. We detail the long-term efficacy of AA observed from the pediatric clinical trial program.
Methods
Efficacy data collected to study completion were pooled from 3 open-label, multicenter investigations of children who manifested HPP signs/symptoms before age 6 months: ages $\leq$3 years (study 002/003 [NCT00744042/NCT01205152]; $n=11$), $\leq$5 years (010-10 [NCT01176266]; $n=69$), and 5–12 years (006/008 [NCT00952484/NCT01203826]; $n=5$). Key assessments included survival, Radiographic Global Impression of Change (RGI-C) score (-3=severe worsening, $+3$=complete/near-complete healing), Rickets Severity Scale (RSS) score (0–10 indicating increasing severity), and growth Z-scores.
Results
Data were from 85 patients (median [min, max]: age at enrollment, 1.3 [0, 12.4] y; average weekly total AA dose, 5.98 [4.0, 11.9] mg/kg; and treatment duration, 2.31 [0, 7.5] y). Probability of survival at 7 years from 002/003 and 010–10 vs. historical controls was 87% vs. 27%. Significant improvement on the RGI-C was documented at Month 3, with the median (min, max) score reaching $+2.0$ ($-1.0, +3.0$; $P<0.0001$; $n=78$) at Month 6, and then sustained through Year 7 ($+2.3$ [$+2.0, +3.0$]; $P=0.001$; $n=11$). Median (min, max) RSS score improved similarly, decreasing from 4.8 (0, 10) at Baseline ($n=82$) to 1.0 (0, 10) at Month 6 ($n=75$) and to 0.5 (0, 5.5) at Year 7 ($n=9$). Growth improved significantly. Median (min, max) Baseline length/height Z-score was -2.91 ($-10.1, +0.9$; $n=83$), increasing $+0.23$ ($-1.9, +6.1$; $P<0.05$; $n=76$) at Month 6, and $+1.01$ ($-3.2, +3.1$; $n=11$) at Year 7. Median (min, max) Baseline weight Z-score was -2.50 (-23.8, 0; $n=84$), increasing $+0.44$ ($-4.9, +6.4$; $P<0.05$; $n=77$) at Month 6 and $+1.67$ ($-2.9, +5.1$; $P<0.05$; $n=11$) at Year 7. Functional outcomes assessed across various scales varied but generally showed cognitive and motor improvement.
Conclusions
In this pooled data analysis of 85 children manifesting signs/symptoms of HPP before age 6 months, AA improved survival, radiographic skeletal manifestations of HPP, and growth. Improvements were observed early on, and sustained over 7 years of treatment.
Disclosure
WH, CRG, MPW, and NB are clinical study investigators and have received honoraria, and/or institutional grant funding/research support, and/or speaker/consulting fees, and/or travel support from Alexion Pharmaceuticals, Inc. AP is an employee of, and may own stock/options, in Alexion Pharmaceuticals, Inc., which sponsored the study. SZ is an employee of Covance, Inc., and provided statistical services for this analysis under contract to Alexion Pharmaceuticals, Inc.

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P78

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P79

Novel imaging approaches to the quantification of musculoskeletal alterations in X-linked hypophosphatemic rickets (XLH)

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Objectives

X-linked hypophosphatemia (XLH) is a rare genetic disorder of phosphate metabolism caused by mutations in the PHEX gene. This pilot study aims to apply novel imaging techniques to asses the musculoskeletal phenotype of XLH patients by bidirectional axial transmission (BDAT) ultrasound, magnetic resonance spectroscopy (MRS) and high resolution peripheral quantitative computed tomography (HR-pQCT).

Methods

BDAT bone ultrasound of the radius and tibia was performed in eight XLH patients aged between 4.2 and 20.8 years and compared to thirthy healthy controls aged between 5.8 and 22.8 years. Nine participants opted to participate in additional HR-pQCT scanning and/or MRS.

Results

Bone ultrasound was feasible in patients and controls as young as 4 years of age. The velocity of the first arriving signal (VFAS) in BDAT ultrasound was significantly lower in XLH patients compared to healthy controls: In the radius, mean VFAS of XLH patients and controls was 3553 ± 196 and 3873 ± 143 m/s, respectively (-8.3%; $P<0.001$). In the tibia, it was 3531 ± 156 and 3757 ± 119 m/s, respectively (-6.0%; $P=0.019$). HR-pQCT showed a higher trabecular thickness in XLH patients ($+16.7\%$; $P=0.021$). By MRS, we found a reduction of intramyocellular lipids in the soleus muscle in XLH patients (-35.4%; $P=0.038$).

Conclusion

BDAT bone ultrasound revealed significant differences in cortical bone quality of young XLH patients as compared to controls. Regular monitoring of XLH patients by a radiation-free technology such as BDAT might provide valuable information on bone quality and contribute to the optimization of treatment. Further studies are needed to establish this affordable and time efficient method in the XLH patient cohort.

Disclosure

The authors declared no competing interests.

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P80

Characterization of pain in patients with fibrous dysplasia

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Pain is common in patients with fibrous dysplasia (FD), however the mechanisms and presentation of pain is poorly understood. Retrospective studies have shown that pain in FD presents along a broad spectrum, responds variably to treatment, and does not correlate with FD disease burden. Pain may be generally conceptualized into two categories: nociceptive pain (associated with actual or potentially tissue damaging stimuli) and neuropathic pain (caused by dysfunction of the somatosensory nervous system). The contribution of nociceptive versus neuropathic pain in FD has not been determined, and it is unknown whether differences in pain type might explain variabilities in the presentation and response to treatment.

Methods

Data were analyzed from 2 FD patient registries: the FD Foundation (FDF) (US) and the RUDY study (UK). Subjects completed questionnaires for neuropathic pain (painDETECT), quality of life (SF-36), and mental health (Hospital Anxiety and Depression Scale) (HADS).

Results

180 subjects in the FDF registry (mean age 38 y, range 8–77, 82% female) and 30 subjects in the RUDY study (mean age 47 y, range 18–71, 73% female) were assessed. Pain types were similar between cohorts: of FDF subjects 46% had nociceptive pain, 32% had neuropathic pain, with 22% unclear, and of RUDY study subjects 47% had nociceptive pain, 33% had neuropathic pain, with 20% unclear. In both cohorts, subjects with neuropathic pain scored significantly lower for general health and physical function on SF-36 ($P<0.05$), and significantly higher for anxiety and depression on HADS ($P<0.05$), in comparison to subjects with nociceptive pain.

Conclusions

Approximately 1/3 of subjects with FD met criteria for neuropathic pain, which was associated with lower quality of life and higher levels of anxiety and depression. These findings were consistent across 2 international cohorts. Evaluation of neuropathic pain should be considered in patients with FD and may inform the development of treatment and monitoring strategies.

Disclosure

The authors declared no competing interests.

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P81

Bone health in adolescent females with anorexia nervosa may be preserved by high lean mass

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Objectives

Anorexia nervosa (AN) is condition of severe low body weight as a result of impaired body image and a fear of gaining weight, often occurring during adolescence, a critical time for bone development. AN has been associated with low bone mass and impaired bone strength. However, many studies have failed to consider body composition, particularly lean mass when assessing bone health. The purpose of this study was to assess if females with AN have an appropriate amount of muscle and bone for their height.

Methods

Twenty adolescent females aged 13–19 with AN were compared with age and height matched controls from the Pediatric Bone Mineral Accrual Study. DXA scans were obtained for total body lean mass and bone mineral content (BMC), as well as hip and spine BMC. Bone variables were compared between groups using independent sample *t*-tests. Z-scores were calculated adjusting for the participant's race, sex, height, weight, actual BMC and predicted BMC using published international pediatric reference standards. Hip structural analysis (HSA) was also applied to all hip scans.

Results

By design there was no significant difference in age and height between groups. Females with AN had a lower body weight (52.3 vs 65.5 kg) and lower body fat (23 vs 33%) ($P<0.05$), but no difference in lean mass. Females with AN were found to have significantly lower total body bone area (1861 vs 1984 cm^2); however, had significantly greater total body aBMD (1.07 vs 1.00 g/cm^2) and lumbar spine area (59.1 vs 51.2 cm^2) ($P<0.05$). AN females had normal BMC z-scores for total body, total hip and lumbar spine ($+0.77$, -0.20, $+0.32$, respectively). HSA analysis revealed a reduced aBMD, increased cross-sectional area, and increased sectional modulus in AN females ($P<0.05$).

Conclusions

We found, on average, females with AN had an adequate amount of bone for their size. In this group there was no difference in lean mass between controls and females with AN. Thus, it may be that a higher lean mass is associated with preserved bone health parameters in this population despite a low body weight and fat mass.

Disclosure

The authors declared no competing interests.

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P82

Tertiary hyperparathyroidism and post-operative hungry bone syndrome in a patient with X-linked hypophosphatemic rickets

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Background
Traditional treatment of X-linked Hypophosphatemic Rickets, while beneficial in minimizing disease associated deformity, is limited by development of treatment related complications, including nephrocalcinosis and hyperparathyroidism.
Presenting problem
A 10-year-old female with XLH rickets was seen for transfer of ongoing care. She had been treated since birth with Calcitriol and phosphate supplement at typical replacement dosing (18 ng/kg/day divided BID and 37 mg/kg/day divided QID, respectively). Initial laboratory investigations at time of first assessment revealed mild hyperparathyroidism and hypercalcemia.
Clinical management
Despite titration of phosphate and calcitriol dosing and eventual discontinuation of all medications, hyperparathyroidism persisted. Parathyroid adenoma was not identified by sestamibi scan or ultrasound. Subtotal parathyroidectomy of 3.5 glands was performed. Post-operatively the patient developed prolonged, severe hypocalcemia lasting 4-weeks consistent with co-existent hungry bone syndrome and hypoparathryoidism.
Discussion
Management of X-linked Hypophosphatemic rickets with conventional therapy is complicated by the potential for iatrogenic complications. We present an XLH patient with tertiary hyperparathyroidism and post-surgical hungry bone syndrome and hypoparathyroidism. Emerging therapies may offer improved outcomes in disease management and prevention of iatrogenic complications.
Disclosure
The authors declared no competing interests.

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P83

Could digital X-ray radiogrammetry be an alternative for dual energy X-ray absorptiometry

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Objectives
Bone mineral density (BMD) in children is generally measured with dual energy X-ray absorptiometry (DXA). Digital X-ray Radiogrammetry (DXR) is a promising alternative technique, that uses BoneXpert software to measure cortical BMD on hand radiographs, expressed as bone health index (BHI). DXR is a cheap method, is easy to apply in every hospital and involves less ionizing radiation compared to DXA. We aim to compare DXR and DXA measurements for determining bone density in children with high probability of secondary low BMD or osteoporosis.
Methods
This prospective study included all children visiting the Radboudumc Amalia Children's hospital between July 2016 and 2018 that underwent both DXA of the lumbar spine (DXALS) and DXR within a 3 months' period. Patients were excluded if either DXALS or DXR could not be assessed. DXA Z-scores were also corrected for bone age (BAZ-scores) with BoneXpert. Low BMD was defined as (BA)Z-score ≤ -2.0. DXR Z-scores were compared to DXA (BA)Z-scores as the golden standard, using Pearson correlations, Bland-Altman analysis and a sensitivity-specificity analysis.
Results
Sixteen (15%) out of 107 patients were excluded, leaving 91 individuals for analyses. Mean bone age, and DXR and DXA (BA)Z-scores, were significantly impaired compared to a healthy reference population. Pearson correlation coefficients were significant between DXR Z-scores and both DXALS (BA)Z-scores: 0.495–0.536 ($P < 0.001$). Bland-Altman analyses showed good agreement between DXR and DXALS (BA)Z-scores. Percentage similarity showed good agreement, mostly for (BA)Z-scores ≤ -2.0. DXR had a sensitivity of 69–71% and specificity of 74–80% compared to DXALS (BA)Z-scores.
Conclusion
DXR correlates well with DXALS (BA)Z-scores and showed good agreement with DXALS, especially for (BA)Z-scores ≤ -2.0. DXR shows best results when compared with DXALS Z-scores. DXR is a promising alternative for diagnosing low BMD in children with high probability of secondary impaired bone density.
Disclosure
The authors declared no competing interests.

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P84

Abstract withdrawn

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P85

Neonatal calcinosis cutis due to a mutation in the GNAS gene

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Background
Calcinosis cutis, the deposition of insoluble calcium salts in the cutaneous and subcutaneous tissue, is rare during infancy. Calcifications are most frequently reported after subcutaneous fat necrosis, hypothermia in neonates or following extravasation of calcium gluconate.
Presenting problem
The patient was born at term by caesarean section because of fetal distress; the birth weight was 2426 g. At age 4 weeks, he was admitted to the hospital due to failure to gain weight. Physical examination revealed calcinosis cutis at the left wrist and forehead. His father had milder skin calcification since childhood.
Clinical management
Serum calcium, phosphate, creatinine, alkaline phosphatase, PTH, 25-hydroxy-vitamin D, TSH and free thyroxine were normal. Whole exome sequencing revealed a heterozygote nonsense mutation in exon 1 of the GNAS gene (NM_001309842: c.91C>T; p.Q31* exon 1/4 stop gain) in the patient and his father. The healthy sister did not carry the mutation. This mutation was previously described as causing pseudohypoparathyroidism.
Discussion
Our case demonstrates the variable clinical phenotype of mutations of this gene and the high index of suspicion required in cases of calcinosis cutis. GNAS mutations should be considered in the differential diagnosis of calcinosis cutis, even as an isolated symptom. The genetic diagnosis provided the family useful medical information for further follow up and management and genetic counseling for future pregnancies.
Disclosure
The authors declared no competing interests.

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P86

Disease-specific pathological traits of youth at risk of secondary osteoporosis as determined through peripheral Quantitative Computed Tomography

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Objectives
This cross-sectional observational study examined peripheral long bone material and structural differences in youth at risk of secondary osteoporosis across disease-specific profiles using peripheral Quantitative Computed Tomography (pQCT).
Methods
Scans of the upper (radius; ulna) and lower (tibia; fibula) limbs of children at 4% distal and 66% mid-shaft sites were undertaken using pQCT. Specific groups were those with (1) increased risk of secondary osteoporosis (neuromuscular disorders [cerebral palsy, Duchenne Muscular Dystrophy and Prolonged immobilisation]; chronic diseases; endocrine diseases; inborn errors of metabolism; iatrogenic conditions), (2) developmental coordination disorder or low motor competence and (3) non-affected controls. Bone outcome parameters included cortical density (CoD), cortical area (CoA), stress-strain index (SSI), total area (ToA), bone strength index (BSI), muscle density (MuD), muscle area (MuA), subcutaneous fat area, fat percentage, endocortical radius, pericortical radius, mid-cortical ring density and trabecular density. General linear models (GLM) with Bonferroni adjustment, controlling for age, sex and bone length examined disease group differences.
Results
Compared to the non-affected controls, children with neuromuscular disorders, developmental coordination disorder or low motor competence had significantly poorer bone parameter outcomes. CoA was significantly lower to the control group for all eight bone sites, with pericortical radius, SSI, ToA, and BSI significantly lower to the control group for seven of the eight bone sites. Endocortical radius, MuA, and mid-cortical ring density were not significantly different to the control group for any bone sites. Other chronic diseases did not show significant differences although small samples were noted for disease groups inborn errors of metabolism ($n=5$) and iatrogenic conditions ($n=12$), despite the 5-year study period.
Conclusion
Neuromuscular disorders and the presence of low motor competence have a strong correlation to bone health for regional appendicular bone parameters in youth at risk of secondary osteoporosis, which suggest a mechanical loading influence. Given that effects of mechanical loading can be seen in regional bone analyses, we conclude that detailed characterisation of peripheral bone health using pQCT has the potential to identify areas for targeted exercise interventions to optimise bone health particularly in patients who present for treatment for other diseases and disorders.
Disclosure
The authors declared no competing interests.
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P87

Assessment of bone density by DXA in poorly controlled children with β-Thalassemia: Correction for hepatic iron - overloadby manual analysis

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Objectives
Beta thalassemia major (BTM) is characterized by anemia and iron overload, especially in children with inadequate chelation therapy. Dual energy x-ray absorptiometry software (DXA) may misanalyse bone measurements due to iron overload/deposition in organs such as the liver. Our objective was to study difference between the anterio-posterior spine measurements of bone mineral content (BMC), area (BA) and density (BMD) in non-chelated beta thalassaemia children with and without inclusion of the liver in the DXA analysis.
Methods
We studied 50 children (2 to 18 year old, 17 girls) with BTM and their anthropometry, haemoglobin and serum ferritin concentrations.AP Spine measurements were performed using a GE iDXA (Wisconsin, MD, USA). With the use of tissue point typing feature of GE iDXA (EnCore software, version 16), analysis was carried out including and excluding the iron overloaded liver. Machine generated Z-scores of L1-L4 BMD were used for analysis.
Results
Mean age of children was 11.6 ± 3.4 years. Mean height and weightfor age Z-scores were -1.8 ± 1.3, -1.6 ± 0.8. Mean Hb and ferritin were 8.2 ± 1.7 g/dl and 1836.3 ± 1478.7 ng/ml respectively.When the liver was included in the tissue point typing during the analysis,mean BMC, BA and BMD at L1–L4 were 19.0 ± 7.6 g, 27.6 ± 6.9 cm^2 and 0.669 ± 0.13 g/cm^2 respectively. After removing the liver from the analysis, the mean BMC (19.9 ± 7.9 g) and BMD (0.702 ± 0.13 g/cm^2) improved significantly ($P<0.05$), the BA remained unchanged. Mean BMD Z-score was -1.64 ± 0.95, which significantly ($P<0.05$) improved to -1.36 ± 1.0 after exclusion of the liver from the analysis.
Conclusion
In poorly chelated children with thalassaemia the inclusion ofiron overloaded liver in the tissue analysis may exaggerate the deficit in bone parameters at AP Spine. Liver should be manually excluded during analysis of the AP spine.
Disclosure
The authors declared no competing interests.
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P88

Diagnostic performance of morphometric vertebral fracture analysis (MXA) in children using a 33-point software programme

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Background
There is significant inter and intraobserver variability in diagnosing vertebral fractures in children. We aimed to evaluate the diagnostic accuracy of morphometric vertebral fracture analysis (MXA) using a 33-point software programme designed for adults, on dual-energy x-ray absorptiometry (DXA) images of children.
Methods
Lateral spine DXA images of 420 children aged between 5 and 18 years were retrospectively reviewed. Vertebral fracture assessment (VFA) by an expert paediatric radiologist using Genant's semiquantitative scoring system served as the gold standard. All 420 DXA scans were analysed by a trained radiographer, using semi-automated software (33-point morphometry). VFA of a random sample of 100 DXA was performed by an experienced paediatric clinical scientist. MXA of a random sample of 30 DXA images were analysed by three paediatric radiologists and the paediatric clinical scientist. Diagnostic accuracy and inter and intraobserver agreement (kappa statistics) were calculated.
Results
Overall sensitivity, specificity, false positive (FP) and false negative (FN) rates for the radiographer using the MXA software were 80%, 90%, 10%, and 20% respectively and for mild fractures alone were 46%, 92%, 8%, and 54% respectively. Overall sensitivity, specificity, FP, and FN rates for the four additional observers using MXA were 89%, 79%, 21%, and 11% respectively and for mild fractures alone were 36%, 86%, 14%, and 64% respectively. Agreement between two expert observers was fair to good for VFA and MXA [kappa = 0.29 to 0.76 (95% CI: 0.17–0.88) and 0.29 to 0.69 (95% CI: 0.17–0.83)] respectively.
Conclusion
MXA using a 33-point technique developed for adults is not a reliable method for the identification of mild vertebral fractures in children. A paediatric standard is required which not only incorporates specific vertebral body height ratios but also the age-related physiological changes in vertebral shape that occur throughout childhood.
Disclosure
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P89

Use of DXA and pQCT measurements to screen for fracture risk in 3 to 18 year old poorly chelated thalassaemic children

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Objectives
Low bone mineral density has been reported in children with beta thalassemia major, they also have increased propensity to fracture. We have studied DXA and pQCT variables in poorly chelated 3 to 18 year old thalassaemic patients and their relationship with fractures in this population.
Methods
We studied 167, 3 to 18 year old children (Girls 72) with beta thalassemia major. Bone measurements were performed by GE iDXA (Lumbar Spine, Total body and vertebral fracture assessment and pQCT (Stratec XCT2000®, Radius 4%). Haemoglobin and serum ferritin were assessed. Fracture history was collected. VFA was carried out by the semiquantitative method described by Crabtree et al (2017). The DXA Lumbar spine and total body measurements were converted to Z-scores using a UK reference dataset. For the pQCT, machine generated Z-scores were used.
Results
The mean age was 11.6 ± 3.9 yrs. The mean height, weight and BMI for age Z-scores were -1.9 ± 1.2, -1.6 ± 0.9 and -0.8 ± 0.9 respectively. The mean Hb and s. ferritin concentrations were 8.1 ± 1.7 g/dl and 2151.3 ± 1894.9 ng/ml respectively. In all, fthere was history of fracture (vertebral or other) in 25% of children (38 with long bone fractures, 3 with vertebral fractures and 3 with both long bone and vertebral fractures). The mean lumbar spine BMAD and total body less head BMD for age Z-scores were significantly lower in fractured than non-fractured children, and were -0.8 ± 1.8 and -0.2 ± 1.5 for LSBMAD and, -2.3 ± 1.2 and -1.4 ± 1.3 for TBLHBMD respectively ($P < 0.05$ for both). The mean trabecular bone density by pQCT for age z-score in fractured than non-fractured group were 1.2 ± 1.5 and 1.8 ± 1.5 respectively. The trabecular density appeared to be high as measured both by DXA (LS BMAD Z-score: majorly trabecular bone) and pQCT (trabecular density z-score) with classifying majority of children above the conventional cut-off of -2 (87% by DXA and 99% by pQCT).
Conclusion
In poorly controlled thalassaemic children DXA but, not pQCT parameters were significantly low in children who suffered fractures. The relatively high trabecular density by pQCT is likely to be due to iron deposition.
Disclosure
The authors declared no competing interests.

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P90

Osteogenesis imperfecta due to FKBP10 mutation- shift from high to low bone turnover

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Background
Osteogenesis imperfecta (OI) due to FKBP10 mutation is a rare variant of OI. FKBP10 encodes for FKBP65, a molecular chaperon that interacts with type I procollagen to prevent premature fibril formation and plays a role in collagen crosslinking. Defects in FKBP65 result in a spectrum of moderate to severe OI with remarkable variability in phenotypes.
Presenting problem
The patient is the first child of non-consanguineous Caucasian parents. She presented with multiple long bone and rib fractures, as well as Wormian bones shortly after birth, consistent with the clinical diagnosis of OI. Bisphosphonate treatment was started at the age of 6 weeks. Molecular studies including testing for COL1A1, COL1A2, CRTAP and LEPRE1 were negative in the early assessment. While receiving regular Pamidronate infusions, she continued to fracture with a total of 24 mainly long bone fractures by the age of 4 years. She showed no deformities or contractures. She started walking at the age of 22 months, other developmental milestones were appropriate. Skin biopsy showed normal collagen formation. Pamidronate treatment was stopped after 4 years. Further genetic testing confirmed a compound heterozygous mutation in the FKBP10 gene c.[310C>T];[944_972del]. 1 year after stopping Pamidronate treatment, her BMD z-score (L1-L4) was $+2.2$, however she continued to fracture and experience bone pain.
Clinical management
She was started on Zoledronate at the age of 6 years. Bone biopsy prior to Zoledronate showed increase in bone turnover. Symptoms did not improve on Zoledronate and treatment was stopped again after 1 year with a BMD z-score of $+2.7$ (L1-L4). Repeat bone biopsy at age 9 years indicated low bone turnover. Additional HRpQCT imaging showed a non-homogenous and trabeculralized cortex, abnormalities in the trabecular struts and rods and periosteal reaction including periosteal fissure with poor mineralization.
Discussion
We present a 9 year old female with severe non-deforming OI due to a compound heterozygous FKBP10 mutation non-responsive to bisphosphonate treatment. Her recent bone biopsy indicates low bone turnover. BMD Z-score and HRpQCT results indicates qualitative rather than quantitative bone impairment. Further medical therapy with an anabolic agent such as growth hormone or possibly PTH is under consideration.
Disclosure
The authors declared no competing interests.

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P91

Bone health index by hand X-ray compared with bone mineral density by dual-energy X-ray absorptiometry in children with Duchenne muscular dystrophy

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Objectives
Children with Duchenne muscular dystrophy (DMD) receiving long-term glucocorticoid (GC) therapy are at risk for osteoporosis and fragility fractures. Recent studies showed that cortical thickness and areas were associated with increased fracture risk. Digital X-ray measurement of the cortical thickness of the metacarpal bones has a potential role as a marker for bone health in children, but has not been evaluated in DMD. The aim of this study was to compare bone age (BA) and Bone Health Index (BHI) automatically computed from hand X-ray with bone mineral density (BMD) parameters obtained by dual-energy X-ray absorptiometry (DXA).
Methods
38 hand radiographs of boys with DMD were retrospectively analyzed by BoneXpert™ (Visiana, Holte, Denmark) to generate automated BA, BHI and Z scores. The BA and BHI data were compared with corresponding DXA measurements (performed on the same day as BA), and clinical variables including age, duration of GC therapy, and fracture history were collected. Linear correlations were performed using Pearson correlation while unpaired two-tailed t-test was used to compare metrics in patients with and without fracture.
Results
Mean chronological age was 12.9 ± 3.9 years. BA and BHI Z scores reduced significantly with age ($r = -0.58$, $r = -0.34$, respectively). BHI Z scores were positively correlated with lumbar spine (LS) BMD height-adjusted (H) Z scores and total body (TB) BMD H Z scores ($r = 0.102$, $r = 0.5$, respectively; $P < 0.01$). BA Z scores were also positively correlated with TB BMD H Z scores ($r = 0.374$), but had a weak negative correlation with LS BMD H Z scores ($r = -0.17$). Patients with history of fractures (24 of 38 or 63%) had significantly lower BA Z scores, lower BHI Z scores, and lower TB BMD H Z scores than those without fractures (-2.3 ± 1.8 vs -0.9 ± 1.6, $P = 0.029$; -2.4 ± 1.1 vs -1.2 ± 1.1, $P = 0.004$; -3.5 ± 2.1 vs -0.95 ± 1.2, $P = 0.0003$, respectively). However, there was no significant difference in LS BMD H Z scores between those with and without fractures.
Conclusions
BHI correlated with DXA readings and also fracture history. BHI can be a useful, low-cost, bone assessment tool in children with DMD.

Disclosure
The authors declared no competing interests.
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P92

A little girl with bowing of legs, a short mother and a waddling sister: Metaphyseal Chondrodysplasia, Schmid type

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Background
Metaphyseal Chondrodysplasia, Schmid Type(MDS) is a rare autosomal dominant disorder characterized by short stature, coxa vara and bow legs, with radiographs showing diffuse metaphyseal flaring and irregularity of tubular bones. We report a family with MDS from Sri Lanka, where diagnosis was made on family history and typical radiographic features.
Presenting problem
A 5-year-old girl presented with asymmetrical bowing of lower limbs since 2½ years of age. She was the second child of non-consanguineous parents. She was born at term by elective caesarian section due to maternal short stature. Birth-weight and length were between 10th–25th centile, and she appeared healthy. At 2½ years she developed bow legs and had been managed as rickets, but shown no improvement with vitamin D therapy. On examination, her weight and height were below 3rd centile, with height within the mid-parental range (mid-parental height 144 cm). She had bilateral genu varus, with the right knee being more affected than the left. It was noted that the mother was very short (138 cm). She had bilateral knee joint pain for several years, but never been evaluated. The elder sibling had a hip problem detected in early life, which was not followed up. There was no other family history of note.
Clinical management
On investigation of the index child, serum calcium, phosphate and alkaline phosphatase and 25-OH-D levels were normal. Lower limb radiographs showed genu varus with metaphyseal flaring and irregularity. Hip and spine radiographs were normal. Skeletal survey of mother and elder sister showed similar radiographic features, and the elder sister had significant coxa vara. A diagnosis of MDS was made in the mother and two girls based on clinical and radiological findings. The family was counselled, and orthopedic referral done. The elder girl subsequently underwent bilateral hip trochanteric epiphysiodesis. The younger girl had spontaneous improvement of genu varus over time.
Discussion
MDS can present in early childhood with clinical and radiological features similar to rickets. A proper clinical approach can help prevent unnecessary interventions and delay in diagnosis, and help institute timely counselling and management to minimize MDS associated complications.
Disclosure
The authors declared no competing interests.
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P93

Assessing the ability of vibration analysis to differentiate wrist and ankle fractures from sprains in children

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Rationale and Hypothesis
Standard practice for differentiating fractures from sprains requires conventional radiographs. Up to 21% of wrist and ankle radiographs in children are negative at a local cost of over £100,000 per annum, approximately £12 million per annum across England and Wales. Our recent pilot study in adults confirmed that vibration analysis in injured patients causes no discomfort.
Objectives
To assess the ability of vibration analysis to differentiate sprains from fractures in children presenting to Emergency Departments following wrist or ankle trauma. To assess patient preference for radiographs or vibration.
Methodology
Prospective consent and recruitment of 100 children presenting to a local Emergency Department following wrist or ankle trauma. All were scanned using the vibration analysis technique before standard radiographs were obtained. Analysis of 50 wrist data sets has been completed using median frequency methods without knowledge of the gold-standard radiographic diagnosis. Analysis of the remaining participants has yet to be completed.
Results
Concerning fractures, 22/23 (95.7%) correctly identified. Concerning sprains, 18/27 (66.7%) were correctly identified. Therefore, vibration analysis would have reduced the number of unnecessary radiographs by 67% at a cost saving of £67,000 locally and roughly £8million across England and Wales per annum. However one patient would have been discharged with a fracture. The questionnaire results were as follows: preferred radiographs 13 (26%); preferred vibration 13 (26%); no preference 24 (48%).
Conclusion
Interim data analysis supports the hypothesis that vibration analysis can be used as an effective screening tool for wrist fractures before radiological exposure and warrants larger studies to explore sensitivity, specificity and further applications.
Disclosure
The authors declared no competing interests.
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P94

Characteristics of ultradistal radius bone density during childhood: results from the Bone Mineral Density in Childhood Study

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Objective
The forearm is a common fracture site during childhood, but DXA pediatric reference data for areal bone mineral density (aBMD) at the ultradistal (UD) radius are lacking. The objective of this study was to first, develop age-, sex-, and ancestry-specific reference data for UD radius aBMD; second, assess the relationship between UD radius aBMD and a) other DXA aBMD measures and b) radius bone volumetric density and geometry by pQCT; and third, examine the tracking of UD radius aBMD over time.
Methods
Data were acquired from the multi-site, longitudinal, Bone Mineral Density in Childhood Study ($n=2014$, 922 males, 22% African American) of healthy children ages 5–19 years at baseline, who provided >10,000 annual DXA measurements over 6 years. In a subset of our cohort ($n=144$), distal radius pQCT scans were acquired at the 3% and 30% sites relative to the distal growth plate. Reference data for UD radius aBMD were generated using the LMS method. Relationships between UD radius aBMD and age, sex, population ancestry, and other bone measures were assessed using mixed effects regression and partial correlations. Tracking from baseline to the 6-year time point was assessed using Pearson's correlations.
Results
UD radius aBMD increased non-linearly with age and was greater in African Americans and males (all $P<0.001$). Age-, sex-, and ancestry-specific UD radius aBMD reference curves were constructed and used to calculate *Z*-scores. UD radius aBMD *Z*-scores correlated positively with total body, lumbar spine, total hip, femoral neck, and distal 1/3 radius aBMD *Z*-scores ($r=0.56$ to 0.64, all $P<0.001$). Partial correlations (accounting for age, age^2, gender and African American ancestry) between UD radius aBMD and pQCT measures of total and trabecular volumetric density were $r=0.53$ and 0.45, ($P<0.001$) respectively. Furthermore, UD radius aBMD *Z*-scores tracked strongly over 6 years ($r=0.69$, all $P<0.05$).
Conclusion
This study provides the first pediatric reference dataset for UD radius aBMD. In contrast to other DXA measures, the UD radius is an appendicular skeletal site comprised of mostly trabecular bone. Given these unique characteristics, UD radius aBMD might provide valuable insight in the clinical setting.
Disclosure
The authors declared no competing interests.
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P95

Detection of intact FGF23 using a novel well-characterized ELISA

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Objectives
Fibroblast growth factor 23 (FGF23) is a bone-derived phosphaturic hormone. The main target organ is the kidney, where FGF23 suppresses renal phosphate reabsorption and vitamin D synthesis. It also stimulates calcium reabsorption in the kidney. FGF23 secretion is stimulated by 1,25(OH)2D and by increased extracellular phosphate concentration, thus forming a feedback loop between kidney and bone. The bioactive intact FGF23 contains 251 amino acids and is glycosylated and phosphorylated. Its activity is mediated by binding to FGFR/Klotho receptor complex at the target cell surface. FGF23 is cleaved between Arg179 and Ser180 to an inactive N- and C-terminal fragment. Increased serum concentrations of intact FGF23 are a hallmark of renal phosphate-wasting diseases such as ADHR, X-linked hypophosphatemia (XLH), tumor-induced osteomalacia, or autosomal recessive hypophosphatemic rickets.
Material
Here, we show the development, characterization and validation of a new ELISA for the determination of intact FGF23. The epitopes of the two monoclonal antibodies utilized in this assay were analyzed by overlapping linear peptides spotted to a microarray. The binding kinetics of the antibodies were determined with biolayer interferometry. The assay was validated according to standard quality guidelines regarding its specificity, precision, robustness, accuracy, and linearity. Assay performance as well as sample measurements of apparently healthy and diseased human subject were compared with other commercially available assays.
Results
The structural epitope of the coating antibody is within the N-terminal part of FGF23, whereas the labelled detection antibody detects a linear epitope at the C-terminal fragment. Both antibodies bind with high affinity to intact FGF23. The immunoassay generates highly specific signals for human intact FGF23 ($>90\%$). Accuracy, parallelism, as well as intra- and inter-assay precision are within the standard of acceptance with 80–120% and $<10\%$ CV, respectively. The intact FGF23 ELISA correlates well with other existing commercial assays ($R^2>0.95$), but shows a broader overall calibration range, a shorter sample incubation and can be used for the detection of FGF23 in human serum and plasma.
Conclusion
This well-characterized ELISA reliably detects intact FGF23 in human serum and plasma samples and may support further high-quality FGF23 research.
Disclosure
Association with Biomedica GmbH.

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P96

Radiofrequency echographic multispectrometry (REMS): a new approach for osteoporosis diagnosis in adolescents

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Objective
Dual-energy X-ray absorptiometry (DXA) is the most commonly used method for evaluating bone mineral density (BMD) in children and adolescents. An innovative echographic approach for osteoporosis diagnosis, directly applicable on both femoral neck and lumbar spine, has been recently introduced and clinically validated through single-center and multicenter studies in a adult population. This developed approach has been subsequently defined as Radiofrequency Echographic Multi Spectrometry (REMS). The main output parameter of this fully non-ionizing technique is BMDUS, a diagnostic index expressed as grams/cm^2, which is measured directly on lumbar vertebrae or proximal femur and has shown significant correlations and good agreement with the corresponding BMD values in adult population. The aim of the study was to evaluate diagnostic accuracy of REMS technology in assessing the bone status at femoral neck and at lumbar spine through the comparison with DXA in adolescents.
Methods
In this preliminary study we evaluate 6 ambulatory adolescents (aged 15.7 ± 1.5 years). All subjects underwent spinal and femoral DXA and echographic scan of the same anatomical sites performed with the REMS approach.
Results
The BMD values by DXA and REMS technique are similar at lumbar spine (Z-score LS by DXA $=-0.37$; Z-score LS by REMS $=-0.37$, $P=$n.s.) and at femoral neck (Z-score LS by DXA $=-0.98$; Z-score LS by REMS $=-0.96$, $P=$n.s.). Moreover, densitometric values provided by the two techniques showed an high degree of Pearson's correlation, with $r=0.90$, $P<0.01$ at femoral neck and $r=0.91$, $P<0.01$ at lumbar spine.
Conclusions
This preliminary study has shown that REMS appears to be an accurate non-ionizing technology able to assess the bone status at lumbar spine and at femoral neck in children and adolescent subjects. The attractiveness of the use of REMS for bone measurements in children and adolescents lies in its lack of ionizing radiation, its ease of use, portability and low cost. However, further studies are needed to establish whether its primary role will be as a complementary measurement or as a replacement for dual-energy x-ray absorptiometry.
Disclosure
The authors declared no competing interests.

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P97

Association of serum alkaline phosphatase with radiological rickets severity in children with X-linked hypophosphataemia on conventional therapy

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Introduction
Conventional treatment of X-linked hypophosphataemic rickets (XLH) involves administration of oral phosphate and vitamin D analogues. An important treatment goal is to heal rickets which is assessed by normalisation of serum alkaline phosphatase (ALP) levels and resolution of radiological signs of rickets.
Objectives
To determine the usefulness of serum ALP in assessing disease severity on wrist and knee radiographs as determined by rickets severity scores (RSS) and Thacher scores.
Methods
Patients from 3 UK tertiary centres, with a confirmed diagnosis of XLH (documented PHEX mutation in the patient or family member) and ≥3 radiographs were included. Data was collected retrospectively from case notes and electronic database. Radiographs were scored for RSS and Thacher scores by a consultant in metabolic bone disease (RP) and radiologist (RS). Due to different assays used for ALP measurements, ALP z scores were calculated using age- and sex-specific mean/standard deviation (s.d.) lab specific reference data. Wilcoxon Signed Ranks test was used to compare knee and wrist RSS. Spearman's correlation was used to determine the relation between ALP z scores and Knee RSS and Thacher scores.
Results
Forty (male$=12$) patients with a median age of 9.3 years (range 0.8–18.9) were identified. Median age at diagnosis was 1.17 years (range 0.2–11.7). The majority (48%, $n=19$) were diagnosed within the first year of life. The median follow-up duration was 7.2 years (range 0.6–18.7). The mean $\pm$ s.d. knee RSS and Thacher score at baseline were 1.9 ± 1.2 ($n=19$) and 3.3 ± 1.3 ($n=8$) respectively and at most recent follow up visit were 1.6 ± 1.0 ($n=26$) and 2.4 ± 1.6 ($n=6$). The mean$\pm$s.d. ALP z score at diagnosis and most recent visit were 4.2 ± 2.9 ($n=36$) and 4.1 ± 2.7 ($n=34$). The wrist RSS was significantly lower than the knee ($P<0.001$). There was no significant correlation between ALP z score and knee RSS ($r=0.17$) or wrist RSS ($r=0.32$) or Thacher scores ($r=0.14$).
Conclusions
1. Conventional therapy was not effective in significantly improving biochemical and radiological features of disease.
2. Lack of association between serum ALP and rickets severity on radiographs limits the value of serum ALP as the sole indicator of rickets activity.

Disclosure
The authors declared no competing interests.

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P98

The effect of vitamin D on bone health assessed by radiogrammetry: a double-blind placebo-controlled vitamin D supplementation trial in infants

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Introduction
The effect of vitamin D± calcium supplementation in children has traditionally been assessed using growth parameters, biochemical markers and radiographs.
Objectives
To evaluate the utility of Bone Health Index (BHI), obtained using automated hand radiogrammetry, in assessing treatment effect in children participating in a vitamin D supplementation trial.
Methods
In this double-blind placebo-controlled trial, Afghan children ($n=3{,}046$) aged 1 to 11 months were randomised to receive six doses of oral vitamin D3 (100,000 IU) or placebo every three months for 18 months. Main outcome variables included 25-hydroxyvitamin D (25OHD), dietary calcium, growth and Thacher rickets severity scores. 25OHD was measured in 120 random subjects (60 per group) at 5 time points. Of the 641 knee and wrist radiographs obtained from a random subset at study completion, 565 wrist radiographs were available for BHI assessment using BoneXpert version 3.0. Groups were compared using linear regression adjusting for covariates where appropriate.
Results
92% (522, male=291) of the images were analysable. The placebo ($n=258$) and vitamin D ($n=264$) groups had similar demographics at baseline. Three months after treatment end (in summer months), placebo and vitamin D groups had comparable 25OHD levels (median 47.5 (40.5 to 55.6) nmol/l vs 50.9 (45.1 to 57.4) nmol/l, $P=0.2$), rickets prevalence (Thacher score >1.5, $n=12$ each), height velocity (10.8 ± 3.1 vs 10.5 ± 3.0 cm/year, $P=0.47$) and height z scores (-2.1 ± 1.1 vs -2.1 ± 1.0, $P=0.60$). Afghan children had a lower mean BHI SDS (-0.35 males, -0.26 female) compared to zero (healthy French reference). There was no significant difference in BHI SDS between placebo and vitamin D groups (-0.30 vs -0.31; $P=0.81$), or between children with and without rickets (-0.64 vs -0.30; $P=0.70$). When adjusted for height z score, BHI SDS correlated positively with calcium intake ($r=0.67$, $P<0.05$). The correlation between BHI SDS and Thacher score was not significant.
Conclusion
Both cohorts were, by enlarge, vitamin D sufficient at study completion and did not differ in BHI SDS or Thacher score. Our data indicate that metacarpal geometry is associated with dietary calcium intake.
Disclosure
The authors declared no competing interests.

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P99

Pre and post-natal achondroplasia, retrospective series of 64 consecutives cases with analyze of the diagnostic methods and timing issues

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The last years, diagnosis of achondroplasia benefited of the recent advances in prenatal imaging (including 3T-CD scan), and in invasive and non-invasive molecular screening.
Objectives
To analyse stage/age, diagnosis procedures and outcome on a series of 64 consecutive cases of achondroplasia, in the French Centre of Reference for skeletal dysplasia, between 2008 and 2016.
Methods
Confirmed achondroplasia were included in this single institution study. Stage of pregnancy/age at diagnosis, analyse of the prevalence of achondroplasia features by imaging (ultrasound, 3D-CT scan), method of molecular confirmation, pregnancy outcome were retrospectively determined.
Results
Sixty-four cases of achondroplasia were included. The diagnosis was made during the pregnancy in 43 cases (67%), in a mean stage of 30 weeks. For the remaining 21 cases (33%), the diagnosis was performed at birth in all cases but one, diagnosed at 2 months. Eight foetuses had at least one parents affected: 4 were diagnosed after early chorionic villus sampling (CVS, 12 weeks), leading to pregnancy termination (PT) and 4 diagnosed after 26 weeks, by ultrasound examination, with uncomplicated birth. In the de novo prenatal 35 cases, ultrasound in the second trimester was normal in 80% of cases. The first symptoms, noticed between 24 and 35 weeks, included femora length reduction (100%), macrocephaly (83%), and hydramnios (17%). The diagnosis was confirmed by the 3D-CT scan in all 17 cases when performed (52%), and/or by molecular screening after amniocentesis (43%) for the common mutation (G380R). Only 1 non-invasive molecular screening was performed in this retrospective series. The prenatal diagnosis led to PT in 12 cases (34%), in a mean stage of 32 weeks. 66% of the foetuses diagnosed in prenatal went into the birth. The comparison between the sub-groups « PT » and « born » showed only a slight but non-significant difference between the stage at diagnosis: 31 weeks versus 29 weeks.
Conclusion
The systematic screening of the second term was normal in 80%. One third of the diagnosis led to pregnancy termination. These results confirm the late diagnosis of de novo achondroplasia during pregnancy, leading to major psychological and ethical issues for the parents.
Disclosure
The authors declared no competing interests.

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P100

High-resolution MRI assessment of the muscle-fat-bone unit in young adults with childhood onset Crohn's disease

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Objective
Childhood onset Crohn's disease (CO-CD) is associated with musculoskeletal deficits. However, there are limited data regarding muscle-bone outcomes in adults with CO-CD. The current study aimed to comprehensively assess the muscle-fat-bone unit in young adults with CO-CD, using novel methods of MRI, in comparison with healthy controls.
Methods
Trabecular microarchitecture and cortical geometry of the distal femur were assessed using 3T microMRI. Muscle cross sectional area (CSA) and fat infiltration (FF) were assessed using six-point VIBE Dixon pulse sequence. CSA was adjusted for FF to measure contractile muscle CSA (CM-CSA). Lumbar spine bone marrow adiposity (BMAT) was measured using ^{1}H-MRS. Grip strength, general health and disease history data were also collected. Results expressed as median (range).
Results
Twenty-six adults with CO-CD (42% male), median age 23.2 years (18.0 to 36.1) and median 10 years (5 to 22) since diagnosis, were compared with 26 age- and gender-matched controls. CD status was in remission (73%) or mildly active

(27%). Apparent trabecular bone volume fraction (0.556 (0.471 to 0.640) vs 0.558 (0.521 to 0.594)), trabecular thickness (0.299 (0.238 to 0.368) vs 0.292 (0.265 to 0.356) mm), trabecular number (1.88 (1.62 to 2.21) vs 1.90 (1.61 to 2.12) /mm), and trabecular separation (0.242 (0.181 to 0.289) vs 0.232 (0.199 to 0.275) mm) were not different between CO-CD and controls, respectively. After adjustment for height, there were no differences in cortical geometry between CO-CD and controls. BMAT was 30.1% (9.6 to 58.8) and 31.3% (11.0 to 68.5) in CO-CD and controls, respectively. CO-CD had 1451 mm^2 (95% CI: 613 – 2289; $P = .001$) lower CM-CSA than controls, after adjustment for sex and height. CO-CD had higher muscle FF than controls (5.2% (0.6 – 9.7) vs 4.1% (0.5 – 9.2); $P = .045$). Grip strength was 5.0 kg (95% CI: 2.1 – 7.9; $P = .001$) lower in CO-CD after adjustment for sex and height.

Conclusion

This high-resolution MRI study found no differences in femur trabecular microarchitecture or cortical geometry between young adults with well controlled CO-CD and healthy controls. However, these subjects had reduced muscle mass, muscle function, and increased muscle fat infiltration in spite of low disease activity.

Disclosure

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P101

Vitamin D levels among Lebnaese children: Do we need to alter normal level?

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Introduction

Vitamin D is essential for calcium metabolism as well as for fracture prevention. In children, low levels can cause rickets. A high prevalence of inadequacy in children has been reported in many studies. It is entirely prevalent in Lebanese children. There are different ways to detect cut-off points for vitamin D deficiency, The aim of this study was to describe the distribution of serum 25(OH) D levels in Lebanese children, males and females, to evaluate and propose new base line for insufficiency among Lebanese children.

Subjects and Methods

Assessment of vitamin D was performed in 574 Lebanese children up to 15 years old. The primary outcome of interest was 25(OH)D level. The reference ranges used in our laboratory for 25-hydroxy vitamin D were as follows: less than 10 ng/ml (deficiency), 10–30 ng/ml (insufficiency) and 30–100 ng/ml (sufficiency). Subjects were divided into groups each of 5 years length.

Results

Age groups, gender and mean Vitamin D serum levels are shown in tables 1 and 2. We consistently found low levels of vitamin D across all age groups in males and females. Our findings showed a low referral rate of males for Vitamin D testing. In both sexes, the prevalence was lowest in subjects aged 11–15 years.

Discussion

A large group of patients fell into the category of insufficiency. Using the reference range of serum vitamin D level proposed by the IOM(Institute of Medicine)in USA: Deficiency <12 ng/ml, Insufficiency 12–19 ng/ml and Sufficient in vitamin D$>$ 20 ng/ml. will shift almost all our patient to the sufficient serum vitamin D levels. We believe that it is important to redefine the vitamin D cut-off across age groups. We require a new clarification systems to assess the vitamin D levels in our population. We need a new base line for insufficiency. Making the cut-off of vitamin D at 20 ng/ml will shift more than two-thirds of Lebanese population to the level of sufficiency.

Disclosure

The authors declared no competing interests.

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P102

Vitamin D deficiency in children in Israel: A cross-sectional study and possible associated factors

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Objectives

This cross-sectional study was done in order to assess the prevalence and determinants of vitamin D deficiency in children taking in account the following parameters: children's age, season, geographic region and ethnicity.

Methods

A cross-sectional prospective study was conducted in Israeli children aged 0–18 from Meuhedet Health Services during the year of 2016 in primary care pediatric clinics throughout all different geographic areas in Israel. Blood samples were obtained from 28,376 patients for serum 25-hydroxyvitamin D [25-OHD] level. Vitamin D deficiency and insufficiency were defined as 25-OHD $<$ 20 ng/ml and <30 ng/ml, respectively.

Results

Vitamin D deficiency was more prevalent in children between 14 and 18 years than in the group of 0–2 years (61.32% and 18.20% respectively, $P < 0.001$) and was directly related to the increase of age. Vitamin D deficiency was more common in winter (57.59%) than in summer (35.34%).

Conclusions

A high prevalence of vitamin D deficiency was found in teenagers in our study, mainly in the group of 14–18 years old and in the winter. These findings are surprising as Israel is a sunny country. Lifestyle and indoors activities may play an important role as associated factors to the Vitamin D deficiency.

Disclosure

The authors declared no competing interests.

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P103

Abstract withdrawn.

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P104

Vitamin D deficiency nutritional rickets presenting to secondary care in children ($<$16 Years) – A United Kingdom surveillance study

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Objectives

Nutritional Rickets (NR) is the commonest cause of rickets worldwide. Although the prevalence of rickets has been widely reported to be increasing, the actual national incidence of NR in the United Kingdom (UK) is unknown.

Methods

Retrospective data were collected monthly between March 2015 and March 2017 from 3500 consultant paediatricians using British Paediatric Surveillance Unit (BPSU) reporting methodology. Clinicians completed an online clinical questionnaire for cases fitting the case definition which were: a) Clinical Rickets – Leg deformity/swollen wrists, knees or ribs and 25OH Vitamin D $<$ 25 nmol/l with one or more abnormalities of serum calcium, alkaline phosphatase, phosphate or parathyroid hormone OR b) Radiological rickets: Widening, cupping, splaying of metaphysis (of any long bone) and 25OH Vitamin D <25 nmol/l.

Results

One hundred and twenty-five cases met the case definition, an annual incidence of 0.48 (95% CI 0.37 to 0.62) per 100,000 children under 16 years. 116 children were under five years, an annual incidence of 1•39 (95% CI 1.05 to 1.81) per 100,000. Boys (70%) were significantly more affected than girls (30%) (OR 2.17, 95% CI 1.25 to 3.78, $P = 0.005$) and the majority were of Black (43%) or South Asian ethnicity (38%). The median age at diagnosis was 18 months. 77.6% of children were not taking vitamin D supplements. Complications included delayed gross motor development (26.4%), fractures (9.6%), hypocalcaemic seizures (8%) and 4 cases of dilated cardiomyopathy (3%) of whom 2 died (1.6%). In a further 8 cases, rickets was confirmed but excluded from the incidence analysis, as not meeting the case definition of a 25OH vitamin D <25 nmol/L.

Conclusion
The incidence of VDD NR in the UK is lower than previously thought. Serious complications and unexpected deaths, particularly in Black and South Asian children under five years have occurred. Both VDD and dietary calcium deficiency are playing a role in its pathogenesis. Uptake of vitamin D supplementation remains low and constitutes a failure of current public health policy. A UK national policy focusing on vitamin D supplementation, dietary calcium intake and adherence is required to eliminate this entirely preventable condition.
Disclosure
The authors declared no competing interests.

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P105

Respiratory health impacts quality of life for adults with OI

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Objectives
Respiratory insufficiency is the leading cause of mortality for individuals diagnosed with Osteogenesis Imperfecta (OI), a skeletal dysplasia clinically characterized by fractures, bone fragility, and scoliosis. The objective of this study is to explore respiratory function and its relation to quality of life, type of OI, presence of scoliosis, stature, and other factors such as age or co-existing co-morbidities.
Methods
Adults with OI completed the SGRQ and provided information through REDCap, including demographics, stature, scoliosis, activity level, and cardiopulmonary comorbidities. Univariate analyses (chi-squared tests, t-tests) and bivariate correlation analyses (Spearman's rho correlation coefficient, point-biserial correlation analysis ($P<0.05$)) were made.
Results
One hundred and fifty-seven adults (108 F, 47 M, 2 FTM) with OI participated. Average age was 45.87 ± 15.51 years. 36% reported having type 1, 25% type 3, 21% type 4, 2% type 5, 2% recessive types, 3% type 3/4, 1% type 1/4, $<1\%$ type 4/5, and 10% with type unknown. 80% reported short stature. 79% reported scoliosis. 41% reported pulmonary comorbidities (asthma, sleep apnea, COPD). 24% reported cardiac comorbidities (hypertension, tachycardia, MVP). Adults with OI scored higher (worse) on average (32 ± 23) than the reference population (6 ± 1). Those with mild type 1 OI scored better than those with moderate type 4 ($P=0.002$) or severe type 3 ($P=0.024$). SGRQ scores correlated with age ($R=0.175$, $P=0.028$), activity level ($R=$-0.248, $P=0.002$), assistive device use ($R=0.280$, $P<.001$), and presence of pulmonary ($R=0.475$, $P<0.001$) or cardiac comorbidities ($R=0.232$, $P<0.001$). There was no correlation with stature or scoliosis, and no sexual dimorphism.
Conclusion
Adults with all types of OI scored higher on the Q17RQ compared to the average population, indicating that social and psychological wellbeing in the OI population is negatively impacted by the higher frequency and severity of respiratory symptoms and resultant activity limitations. People with all types of OI are impacted by their respiratory health independent of cardiopulmonary comorbidities, scoliosis, or stature.
Disclosure
Advisory Board or Panel. Alexion - Speaker's Bureau. Ascendis - Advisory Board or Panel.

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P106

Scoliosis and cardiopulmonary outcomes in adults with osteogenesis imperfecta: a pilot study

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Objectives
Osteogenesis imperfecta (OI) is a group of rare genetic disorders characterized by osteoporosis, predisposition to fracture, and scoliosis. Recently, however, there has been increased focus on pulmonary insufficiency, as it is the leading cause of mortality in individuals with OI. The primary objective of this study is to determine if reduced pulmonary function in individuals with OI is intrinsic to the underlying connective tissue disorder. Another goal of this study is to explore respiratory function and assess how it relates to type of OI, presence of scoliosis/chest wall deformity, and other factors such as age or co-existing co-morbidities.
Methods
This is a prospective pilot study of adults diagnosed with OI. Anteroposterior X-rays were evaluated for scoliosis (curve $>10^{\circ}$). The largest curve was used for analysis. Pulmonary function (FEV1/FVC) was defined as restrictive disease $>80\%$, and obstructive disease $<70\%$. Chest CTs were qualitatively evaluated for evidence of lung disease. Echocardiograms and EKG were obtained to assess cardiac health. Bivariate correlation analyses (Spearman's rho correlation coefficient and point-biserial correlation analysis ($P<0.05$)) were performed.
Results
Twenty-six individuals with OI were enrolled (77% female, 23% male). Mean age was 39 ± 15 years. 19% had type 3, 46% type 4, and 35% type 1. 57% had scoliosis, 14% had cardiac comorbidities, and 7% had pulmonary comorbidities. 90% of chest CTs revealed abnormalities (bronchial wall thickening, parenchymal scarring, ground-glass opacities, air trapping). 52% of EKGs showed abnormal results (tachycardia, non-specific wave abnormalities). 77% had trace mitral, tricuspid, or aortic regurgitation on echo. There was no correlation between curve magnitude and pulmonary function ($R=0.136$, $P=0.509$).
Conclusion
Pulmonary function is weakly correlated with curve magnitude, suggesting that decreased pulmonary function is likely due to intrinsic lung disease - not exclusively an effect of scoliosis. This mandates reassessment of clinical practice in evaluating cardiopulmonary health of these individuals. This study was made possible through the OI Foundation's Jamie Kendall Fund for OI Adult Health.
Disclosure
Advisory Board or Panel. Alexion - Speaker's Bureau. Ascendis - Advisory Board or Panel.

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P107

Sex differences in the longitudinal associations between body composition and bone stiffness index in European children and adolescents

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Objectives
The present study aims to evaluate the longitudinal association of fat mass (FM), fat free mass (FFM) with bone stiffness index (BSI) in European children and adolescents over 2 and 6 years follow-up. METHODS: We included children of the IDEFICS/I. Family cohort, who participated in repeated measurements of BSI using calcaneal quantitative ultrasound (QUS), body composition using skinfold thickness, sedentary behaviours (SB) and physical activity (PA) using self-administrated questionnaires. Regression coefficients (β) and 99%-confidence

intervals (99%CI) were calculated by sex-specified generalized linear mixed effects models to analyse the longitudinal relationships between body composition z-scores and BSI percentiles, as well as to explore the possible interactions between body composition z-scores and pubertal status.
Results
Of 2468 participants, 1274 (51.6%) were male. The baseline zFFM was positively associated with 2 years change of BSI percentile in boys ($\beta = 3.86$, 99%CI: 1.69, 6.03). Furthermore, both the baseline zFFM ($\beta = 7.30$, 99% CI: 3.48, 11.12 in boys and $\beta = 3.45$, 99%CI: -0.07, 6.97 in girls) as well as 6 years change of zFFM ($\beta = 6.90$, 99%CI: 2.12, 11.68 in boys and $\beta = 4.87$, 99%CI: 0.30, 9.44 in girls) seem to be positive predictors for the 6 years change of BSI percentile. In contrast, a negative association between 6 years change of zFM and BSI percentile was observed in boys ($\beta = -3.76$, 99% CI: -7.04, -0.47). Moreover, we observed an interaction between 6 years change of zFM with pubertal status (assessed at follow-up) on the 6 years change of BSI percentile in girls ($P = 0.007$).
Conclusions
Our finding supports the existing evidences for a positive relationship between FFM and BSI. Additionally, it seems that long-term FM gain is inversely associated with BSI in boys, whereas opposing associations were observed across different pubertal status in girls. Further bone health intervention programs among youth should focus on increasing FFM instead of improving weight status, and take sex and pubertal status into consideration.
Funding
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Disclosure
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P108

Abstract withdrawn

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P109

Fracture prevalence in children 0–19 years-old in Mexico: A 10-year cross-sectional analysis

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Fracture prevalence in children appears to change in recent years due to variations in physical activity and enforcement of laws that protect children within motor vehicles. However, in Mexico such variation has not been explored so far.
Objective
To analyze fracture prevalence in the paediatric population of Mexico to detect patterns of change in time, between genres and among different diagnoses.
Methods
We analyzed data from the main Social Security system in the country (IMSS) using data of fractures in children 0–19 years-old from 2007 to 2017 to look for trends in general fracture rate, differences between genres and different types of fractures. IMSS uses ICD10 to code fractures, we obtained the number of cases for each diagnosis divided by the total number of affiliates grouped by ages (0–4, 5–9, 10–14 and 15–19 years-old) to obtain prevalences.
Results
Total prevalence of fractures in children ages 0 to 19 decreased from 0.942/10000 in 2007 to 0.758/10000 in 2017. This trend is due to decrease in fractures of skull and face (S02), ribs and sternum (S22) and to a minor extent shoulders and arm (S42). Lower limb fractures like femur (S72) leg and ankle (S82) show no significant changes in time. Year-to-year analysis by groups of age showed a pattern: Increases prevalence of fractures in boys as they age, as well as decreasing prevalence in girls as they reach puberty.
Conclusions
This analysis is a first glance at information needed to evaluate the trends in fractures en Mexico. While one of the limitations of this data is the lack of knowledge about mechanisms of lesion and the place where they took place, it is a first step to analyze changes in habits and better protection of children in certain environments, such as motor vehicles, and the relationship with fracture prevalence.
Disclosure
The authors declared no competing interests.
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P110

Cost-effectiveness of a Vitamin D supplementation programme in pregnant women and children to prevent rickets in the UK

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Introduction
Rickets is characterised by defective mineralisation of the growth plate and osteoid, caused by deficiency of vitamin-D and/or of dietary calcium. Rickets continues to be reported in the UK, especially in children from dark-skinned ethnic groups. Literature on the cost of management of rickets and cost-effectiveness of vitamin D supplementation is lacking worldwide.
Methods
The analysis considers the cost-effectiveness of an intervention in five groups of skin pigmentation (whole population, white, light, dark and combination of light and dark), where vitamin-D supplements would be provided free of charge to children aged 0–4 years and pregnant women in order to prevent rickets in comparison to no supplementation. Analysis was conducted in the Central Manchester area where all cases of rickets from 1-January-2009 to 31-December-2014 were identified. Cost of management of rickets was calculated from National Health Service, UK tariffs. Rickets prevalence estimates were calculated using census data from 2011. Quality of life was assessed using counterfactual utility estimates gathered from a systematic literature review and population baseline utility. Intervention efficacy was gathered from literature reporting similar intervention implemented in Birmingham. Incremental cost effectiveness ratio (ICER) was also calculated for Quality-Adjusted Life Years (QALYs) gain threshold of £20–30,000, which is a yardstick used by the National Institute for Health Care Excellence, UK when evaluating cost-effectiveness of new or existing drugs/technology.
Results
During the study period, 57 children were managed for rickets of which 26 were dark and 29 were light skin pigmented. Rickets incidence was 29.75/year/100,000 children under 4 years. Average cost of management of rickets was related to associated complications and was highest in dark-skinned children (£7,305). ICER for dark-skinned children and pregnant women was $<$£0 and within the QALY threshold. Therefore, cost-effective and budget-saving. In other groups ICER did not cross the threshold (white = £1,352,599, light = £64,375) and, therefore, not cost-effective. On combining data for light and dark pigmented children and pregnant women, ICER was marginally above the QALY threshold of £33,131.
Conclusion
Vitamin-D supplementation for dark-skinned children and pregnant women, but not for the wider UK population, seems to be cost-effective in preventing rickets as per the QALYs gained.
Disclosure
Only data collection was supported by Internis pharma.
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P111

Vitamin D dependent rickets type 1 caused by CYP27B1 mutation

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Objectives
Vitamin D dependent rickets type I (VDDR-I) is an autosomal recessive disorder with impaired activation of vitamin D, caused by mutations in CYP27B1. Characteristic clinical features are hypotonia, muscle weakness, growth failure, hypocalcemic seizures in early infancy, and radiographic findings of rickets. We aimed to describe the clinical and laboratory findings in a VDDR-1 case and to report a mutation in CYP27B1.
Methods and results
The patient was admitted with seizure at the age of 14 months. Blood calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), 25(OH) vitamin D, and 1,25(OH)2 vitamin D levels were 5.1 mg/dl, 3.7 mg/dl, 705 IU/l, 429 pg/ml, 24.9 ng/ml, and 8.8 pg/ml, respectively. Radiological findings included cupping and fraying of the radial and ulnar metaphysis. On molecular genetic study, the patient revealed a compound heterozygous mutation for the 7-bp duplication 1319-1325dupCCCACCC (Phe443Profs*24) and IVS3+1 G>A in the CYP27B1 gene. Analysis of the family members showed that the asymptomatic mother and sister were heterozygous mutations for IVS3+1 G>A, and the father was heterozygous for the Phe443Profs*24. The patient was treated with calcium lactate and calcitriol.
Conclusion
Until now, five Korean patients with VDDR-I have been studied and three distinct mutations have been identified. The splice site mutation, IVS3+1 G>A, occurred in 5 of 10 alleles, the Phe443Profs*24 occurred in four alleles and the 2561G>A (W328X) mutation in exon 6 occurred only one allele. This patient showed a compound heterozygosity for IVS3+1 G>A and Phe443Profs*24 mutation. So, Korean patients with VDDR-I revealed only three different mutations in 12 alleles, suggesting that the genetic defect in the CYP27B1 gene is homogeneous in Korean ethnic group.
Disclosure
The authors declared no competing interests.

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P112

Case report: investigation of an osteolytic lesion leading to the diagnosis of congenital generalized lipodystrophy due to a novel AGPAT2 mutation

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Background
Osteolytic lesions can be the presenting manifestation of various medical conditions, including bone tumors (benign and malignant) and infectious and endocrine diseases.
Presenting problem
A 19-year-old Bedouin male from a consanguineous family was referred to our medical center for orthopedic consultation due to a pathological fracture and a cystic lesion in his right ulna. A skeletal survey revealed another cystic lesion in the left tibia. A SPECT bone scan ruled out additional bone pathology. A bone biopsy revealed normal cortical bone with no evidence of malignancy. During hospitalization he was referred for endocrine evaluation due to poorly controlled diabetes.
Clinical management
Physical examination revealed prominent muscles, an acromegaloid appearance, marked acanthosis nigricans, and skin papillomatosis. Anthropometric measurements: height 170 cm, weight 77.2 kg, and BMI 26.3 kg/m^2. Body composition (bioelectrical impedance scale): 13% fat (normal range 10–20%), muscle mass 63.6 kg (49.7–63 kg), normal estimated bone mass 3.3 kg, basal metabolic rate 2000 kcal, and a muscular physique.
Laboratory evaluation
Diabetes with severe insulin resistance (fasting glucose 189 mg/dl [10.5 mmol/l], fasting insulin 70.95 μu/ml, HOMA-IR 33). Comorbidities: dyslipidemia with mildly elevated triglycerides 177 mg/dl (elevated ≥150 mg/dl), and low high-density lipoprotein 29 mg/dl (normal in males >40 mg/dl), non-alcoholic fatty liver disease – hepatic fat deposition with moderate fibrosis, and microalbuminuria. There was no evidence of heart disease. The clinical phenotypic features were highly suggestive of congenital generalized lipodystrophy due to AGPAT2 mutation. Undetectable serum leptin levels supported this diagnosis. Next-Generation Sequencing targeting the AGPAT2 gene identified a novel homozygous frameshift mutation. Deterioration of glycemic control with progressive increase in insulin requirements to 7 Units/kg per day led to initiation of metreleptin (recombinant human methionyl leptin). Leptin replacement therapy, the only medication approved specifically for lipodystrophy, resulted in a remarkable improvement in glycemic control and reduction in insulin requirements, with no change in the osteolytic long bone lesions.
Discussion
Congenital generalized lipodystrophy syndromes comprise a rare, heterogeneous group of conditions characterized by a distinctive muscular physique. Osteolytic lesions in long bones in the context of lipodystrophy point towards the diagnosis of AGPAT2 gene mutations. The precise diagnosis enables the clinician to avoid unnecessary invasive procedures and provide appropriate management.
Disclosure
The authors declared no competing interests.

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P113

Next-generation sequence and biomarker levels in the patients with early-onset chronic non-bacterial osteomyelitis from North Caucasian region of Russia

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Objectives
Chronic non-bacterial osteomyelitis (CNO) is a heterogenic group of immune-mediated inflammatory bone diseases with unclear pathogenesis. Only a few genes associated with this condition have identified. The aim of the study was to evaluate the spectrum of mutations in genes associated with primary immunodeficiency syndromes (PIDs) and autoinflammatory diseases (AIDs) in the cohort of patients with early-onset CNO from North Caucasus (Dagestan and Chechnya) and assessment of new biomarkers.
Methods
We selected a subgroup of the CNO patients ($n=22$) having the following features: 1) early disease onset (<5 years); 2) all children were initially diagnosed as having tuberculosis (TB) due to bone morphology findings (granulomatosis, e.g. tuberculosis-like inflammation), but had negative TB culture test; 3) initial treatment with a combination of 3–4 anti-MBT drugs during 1–2 years was ineffective, and the patient continued to develop new inflammatory bone foci; 4) all patients were from areas with traditionally high prevalence of consanguinity. Targeted next-generation sequencing analysis of 302 genes related to PIDs and AIDs was performed. In each patient, we evaluated calprotectin, interleukin-6, and 14-3-3 protein level. Control group were five healthy children.
Results
Rare variants of PID genes were detected in 7/22 (32%) patients. Mutations affecting the genes previously associated with CNO were found only in two patients: one of them carried heterozygous variant IL1RN c.170G>T (p.C57F), and another had IL1RN c.512T>C (p.V171A). No mutation of LPIN2 was revealed. Other detected variants included one pathogenic MEFV p.M694V mutation in the heterozygous state and some VUS in CD40LG, NLRP12, CR2, NLRP3, IL12B, PLCG2, SH3BP2, CARD14, IRF8, CASP10, and NFKB1A genes. In CNO patients levels of calprotectin was 5.9 (5.2–6.7) vs 0.75 (0.68–0.84) ng/ml, $P=0.000003$; interleukin-6 – 45.5 (40.0–51.0) vs 4.0 (3.2–4.9) ng/ml, $P=0.000003$; 14-3-3 protein – 19.9 (18.3–27.1) vs 2.4 (1.5–5.1) ng/ml, $P=0.0000003$ compare to controls.
Conclusion
Mutations in known genes were detected only in a minor fraction of CNO patients from Dagestan and Chechnya. Further investigations required for biomarkers validation.

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Disclosure
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P114

Hypophosphatasia in Japan: ALPL mutation analysis in 98 patients
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Background
Hypophosphatasia (HPP) is caused by inactivating mutations in the ALPL gene encoding tissue-nonspecific alkaline phosphatase (TNSALP). HPP is variable in clinical manifestations and prognosis, and is generally classified into six subtypes: perinatal lethal, perinatal benign (prenatal benign), infantile, childhood, adult, and odonto HPP. Although genetic test is broadly used for diagnosis of HPP, the genotype-phenotype relationship still remains unclear.
Objectives
We aimed to clarify the features of Japanese HPP and the relationship between ALPL mutations and the clinical manifestations.
Methods
We analyzed 98 unrelated Japanese patients of HPP, whose ALPL mutations had been identified in Osaka Women's and Children's Hospital, since 1996 to 2018. Novel mutations were characterized by transfection of the expression plasmids into COS-7 cells.
Results
Clinical classification of the 98 patients was as follows: 45 patients (45.9%) with perinatal lethal, 22 patients (22.4%) with perinatal benign, 12 patients (12.2%) with infantile, 3 patients (3.1%) with childhood, 1 patient (1%) with adult, and 14 patients (14.3%) with odonto HPP. There was 1 aborted patient (1%). Among the 196 ALPL alleles, c.1559delT was found in 89 alleles (45.4%) and was the most frequent. All of c.1559delT homozygotes were classified into perinatal lethal form. The second most frequent mutation was p.F327L and was detected in 23 alleles (11.7%). The third most frequent mutation was p.F327del (5 alleles; 5.1%). All of the 22 patients with perinatal benign HPP were compound heterozygous for ALPL mutations, and 19 out of them had p.F327L. The 1 adult form and 7 out of 14 patients with odonto HPP were positive for only one mutations, and we confirmed the dominant negative effects in some of the mutant proteins associated with autosomal dominant HPP.
Conclusion
More than 60% of Japanese HPP are perinatal onset. High frequency of perinatal benign HPP is characteristic. As we previous reported, c.1559delT is the most frequent mutation and p.F327L is the second most. The high prevalence of these mutations may underlie the high rate of perinatal lethal and perinatal benign HPP, respectively. Identification of ALPL mutations is beneficial for evaluation of severity and prediction of prognosis in Japanese HPP.
Disclosure
The authors declared no competing interests.
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P115

Mabry Syndrome is a cause of hyperphosphatasia and mental retardation
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Background
Hyperphosphatasia may be seen in liver disorders or metabolic bone disease with the most common cause likely to be Vitamin D deficiency. However, we report the case of child who had high ALP levels from infancy along with intellectual retardation. Genetic testing revealed Mabry Syndrome.
Presenting problem
At birth, a micrognanthia and a cleft palate was apparent. She went to have developmental delay, impaired vision, and was wheelchair dependent. She had a working diagnosis of Pierre Robin Sequence. There was no bone pain, spinal tenderness or any fracture history. There was adequate calcium in her diet.
Results
The ALP was elevated from birth with levels persistently around 2000iu/L (100-400). The calcium and phosphate were always normal, the Vitamin D levels were often very low (<20 nmol/L), with a PTH level either in the normal or just above the normal range. She had regular treatment with Vitamin D, including an intramuscular injection. Bone specific ALP was markedly raised, but this test coincided with severe Vitamin D deficiency. A skeletal survey was taken at 8 years of age. Apart from a scoliosis, it did not show any skeletal dysplasia or features of juvenile Paget's disease. She had a further opinion at 9 years of age and a diagnosis of Mabry syndrome was considered. Genetic Testing showed she was homozygous for the pathogenic PGAP3 mutation c182-2A$>$G which is known to cause hyperphosphatasia with mental retardation syndrome 4 (HPMRS4).
Discussion
Mabry syndrome is a rare autosomal recessive condition caused by an impairment of glycosylphophatidylinositol biosynthesis resulting in high ALP levels. It is characterized by elevated serum alkaline phosphatase, severe psychomotor developmental delay, seizures, and facial dysmorphism. Fractures, camptodactyly, truncal obesity, and hyperpigmented macules have been described. In patients with persistent unexplained hyperphosphatasia and mental retardation, genetic testing for Mabry syndrome should be considered.
Disclosure
The authors declared no competing interests.
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P116

Molecular genetic diagnosis and genotype-phenotype correlations in children and adolescents with recurrent fractures
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Objectives
To evaluate the diagnostic outcomes of massively parallel sequencing (MPS) and identify genotype-phenotype correlations in children and adolescents with recurrent fractures.
Methods
A retrospective chart audit was conducted of children and adolescents referred to the endocrine clinic at a tertiary children's referral hospital with a history of recurrent fractures. Phenotypic data including fracture history, bone mineral density (BMD) and biochemistry for bone/mineral homeostasis were collected. MPS for a brittle bone panel of 13 genes was also undertaken. Statistical analysis was performed using SPSS software to determine a correlation between genotype and phenotypic variables.
Results
The study population comprised 83 individuals. Of these, 24 (29%) were noted to have clinically diagnostic features of OI and were characterised as a separate group for analysis. Out of the 59 remaining patients, 36 (61%) had normal genetic testing, 17 (29%) had a variant of unknown significance (VOUS), 5 (8%) were heterozygous for pathogenic LRP5 mutations and 1 (2%) had a pathogenic COL1A2 mutation. VOUS were identified in COL1A1, FKBP10, PLOD2, LRP5, CRTAP, SERPINH1, SERPINF1, and P3H1. There was no correlation between positive mutation detection and type of fracture, number of fractures or BMD variables.
Conclusion
There was no significant correlation between MPS result and patient phenotype in those without a clinical diagnosis of OI. Although the diagnostic yield of MPS from those without clinical features of OI was low, there remain a significant number of identified mutations in this group suggesting a low threshold for genetic testing. Functional studies are underway to determine the pathogenicity of the large number of VOUS detected by MPS. These data may help elucidate which children would benefit from molecular genetic testing.
Disclosure
The authors declared no competing interests.
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P117

Use of Lego® to explain genetic variations in type 1 collagen – a pilot study

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Objectives
To examine the usefulness of Lego® as a visual reinforcer to explain genetic mutations to parents and carers of children and young people who have osteogenesis imperfecta (OI).
Methods
Before entering a dedicated OI clinic, patients and carers completed a quantitative questionnaire devised by one of the team (MR), asking how much they knew about the genetic mutations causing OI within their families and whether they wished for a more detailed explanation. If so, an explanation using Lego® bricks to represent the 'spelling mistake' and its impact was given by a consultant (JA), who is not a geneticist. This explanation involved the use of four different coloured small (1×1 or 1×2) bricks to represent the four different codons, together with a variety of different coloured flat bricks (3×1) to represent the different amino acids. Using this method, it was possible to explain all major mutations including single base substitutions, insertions, deletions, intronic mutations/splice site variations, pro-peptide sequence variations and whole exon deletions etc. An adapted questionnaire collecting additional qualitative data was completed by the parent/carer after leaving the clinic. Responses were scored on a visual analogue scale with scores between 0 and 10. Paired t-test was used for statistical analysis and qualitative data recorded.
Results
Fourteen patients expressed an interest in having further information about their genetic mutation and all completed both pre- and post-clinic questionnaires. As expected, the most common mutation was a single base pair substitution resulting in a single glycine substitution with impaired cross-linking between individual collagen strands, but all of the above variations were included. The mean score (Range) prior to explanation was 3.0 (1–7) and this rose to 8.4 (6–10) afterwards ($P<0.01$). In no subjects did the score decline. Positive qualitative responses (13) were included.
Conclusions
All subjects expressed an increased understanding of their genetic variations and many said that they found the visual approach very helpful. We therefore intend to extend this methodology to larger numbers both within the OI and other clinics and to assess the extent to which the information is retained at a future time point.
Disclosure
The authors declared no competing interests.

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P118

Methyl-CpG-binding protein 2 (MECP2) mutation type is associated with bone disease severity in Rett syndrome

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Objective
Rett syndrome (RTT) is an X-linked neurodevelopment disorder. More than 95% of RTT female have mutations in methyl-CpG-binding protein 2 (MECP2), whose protein product modulates gene transcription. Specific MECP2 mutations may lead phenotypic variability and different degrees of disease severity. It is known that low bone mass is a frequent complication of subjects with Rett syndrome. This study aimed to investigate if specific MECP2 mutations may affects the degree of involvement of the bone status in Rett subjects.
Methods
The study cohort consisted of a group of 227 well defined RTT females (aged 2–38 yrs). Diagnosis of RTT was based on the consensus criteria for RTT and molecular confirmation. In all subjects bone mineral density at whole body (BMD-WB) and at femur (BMD-FN and BMD-TH) were measured. QUS parameters were assessed at phalanxes (AD-SoS and BTT). Moreover, ambulation capacity, fracture history and presence of scoliosis were assessed.
Results
In agreement with literature data, we consider the most eight common point mutations: R106W $N=3$; R133C $N=14$; T158M $N=27$; R168X $N=17$; R255X $N=16$; R270X $N=22$; R294W $N=10$; R306C $N=13$. We divided the subjects with the most common point mutations in two group based on genotype-phenotype severity; in particular, there has been consensus in recognising that the mutations T158M, R168X, R255X, R270X are considered more severe. BMD-WB, BMD-FN and BMD-TH were lower in RTT subjects that present the most severe mutations with respect to less severe mutations, but the difference was statistically significant only for BMD-TH Z-score (-3.44 ± 1.18 vs -1.75 ± 1.99; $P<0.05$). Also both AD-SoS and BTT values were lower in subjects that present the most severe mutations but the difference was not statistically significant. Moreover, RTT females with more severe mutations present a higher prevalence of scoliosis (60.0% vs 36.7%; $P<0.05$) and of inability to walk (77.1% vs 51.7%; $P<0.05$).
Conclusion
This study confirms that MECP2 mutation type is a strong predictor of disease severity in Rett subjects. In particular, the subjects with more severe mutation present a greater deterioration of bone status, and a higher prevalence of scoliosis and inability to walk.
Disclosure
The authors declared no competing interests.

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P119

A novel mutation in FAM111A gene in child with Kenny-Caffey syndrome type 2 presenting with short statue, medullary stenosis and hypoparathyroidism

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Background
Congenital hypoparathyroidism in children is a condition with diverse genetic etiologies. Kenny-Caffey syndrome (KCS) is a rare genetic disorder characterized by hypoparathyroidism, short stature, cortical thickening and medullary stenosis of the tubular bone and dysmorphic features including micrognathia, prominent forehead and eye abnormalities. The autosomal dominant form of KCS [KCS type 2(KCS2)] is differenced from autosomal recessive form of KCS [KCS type 1 (KCS1)] which is caused by mutation of tubulin-folding cofactor E (TBCE) gene, by the absence of intellectual disability. Presenting problem. A 6-year-old boy was born 2,850 gm at 40 weeks of gestation to nonconsanguineous Thai parents. At 1 month of age, he was referred to pediatric endocrinologist because of recurrent generalized convulsion due to hypocalcemia. At this time, his serum Ca, P, Mg, intact PTH levels were 4.3, 8.8, 1.34 mg/dl and 5.5 pg/ml, respectively. Calcium and oral calcitriol administration were started on the basic of diagnosis of primary hypoparathyroidism. At 5 years his height, weight and head circumference were 89.2 cm (-4.4 S.D.), 13.3 kg (-2.5 S.D.) and 48.1 cm (-2.2 S.D.), respectively. He had normal intelligence for his age. Bone survey was done in this case showed medullary stenosis and cortical thickening. He was diagnosed with KCS2 based on clinical finding of hypoparathyroidism, proportionate short stature, and medullary stenosis revealed by radiography.
Clinical management
We obtained peripheral blood sample from this patient with inform consent of DNA analysis. A novel heterozygous missense pathogenic variant c.1670C>G (p.Ala557Gly), chr11:58920811) in the FAM111A gene was identified in the patient. Pathogenic variant in this gene is known to cause Kenny-Caffey syndrome type 2. His parents do not have this variant.
Discussion
In the present study, we identified novel mutation of FAM111A as the gene responsible for KCS2 by applying an exome sequencing strategy. FAM111A constitutively expressed in parathyroid gland and bone may have a role affecting parathyroid gland development and intracellular pathways regulating normal skeletal development and height gain.
Disclosure
The authors declared no competing interests.

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P120

Mutational and phenotypic spectra in 137 Russian patients with inherited forms of rickets

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Background
Inherited forms of rickets are metabolic bone diseases developing as a result of inadequate mineralization of a growing bone due to disruption of calcium, phosphorus and/or vitamin D metabolism. Diverse phenotypic presentation and aetiology of these disorders pose difficulties for the diagnosis and management.
Objective and hypotheses
The aim of this study was to perform molecular diagnostics and clinically characterize 137 patients with hereditary forms of rickets.
Method
One hundred and thirty-seven patients were included if they showed clinical and biochemical features compatible with the diagnosis of rickets (namely, low serum calcium and/or phosphate, increased serum levels of alkaline phosphatase, high or normal PTH, and low tubular reabsorption of phosphate). 'Rickets panel' genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent). Bioinformatics analysis was performed using Torrent Suite (Ion Torrent) and ANNOVAR (annovar.openbioinformatics.org) software packages.
Results
The study showed that most patients ($n=126$) were diagnosed with hypophosphatemic rickets (HR), including 66 familial and 60 sporadic cases. The mean age at diagnosis was 7.5 years [0,2;17]. Clinical symptoms of HR included: deformities of leg bones (90%), muscle weakness (75%), multiple dental abscesses (72%) and short stature (52%). The most severe short stature was noted in patients after multiple osteotomies: Me height -3.07 [-3.85; -2.21] ($n=42$). Mutations were identified in 84% of cases with HR: PHEX ($n=106$), FGF23 ($n=1$), CLCN5 ($n=1$) and SLC34A3 ($n=1$). In 19 probands no mutations were detected, however, one patient was diagnosed with tumor-induced osteomalacia and two patients had cutaneous skeletal hypophosphatemia syndrome. 11 patients were diagnosed with vitamin D-dependent rickets. In 5 probands mutations were detected in CYP27B1 gene, 3 probands had VDR mutations and in 3 probands no mutations were detected.
Conclusion
The study confirmed predominance of HR caused by PHEX mutations among patients with inherited forms of rickets. Surgery before puberty in patients with HR is associated with a high risk of recurrence of the limb deformity and negative impact on patients' final height. Early genetic diagnostic helps to start adequate treatment on time, which improves quality of life for patients with inherited forms of rickets.
Disclosure
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P121

An Acvr1[R258G] 'conditional on' mouse model of atypical fibrodysplasia ossificans progressiva (FOP) is Activin A dependent

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FOP is an autosomal dominant disorder characterized by early onset, episodic and progressive ossification of skeletal muscle and associated connective tissue. FOP is driven by mutations in the intracellular domain of ACVR1 (ALK2), the most common of which is R206H. However, rare FOP causing mutations exist throughout the GS and the kinase domain of Acvr1. Several of these mutations result what appears to be a more severe FOP phenotype that includes significant developmental abnormalities in addition to the postnatal heterotopic bone formation. Two unrelated individuals with one such mutation, R258G, in the kinase domain of Acvr1 have a severe phenotype (Kaplan *et al*. 2015). We have modeled this mutation to investigate whether it results in a more severe phenotype in a mouse when present in the same genetic background as the more common R206H mutation. We engineered a Cre-regulated 'conditional-ON' allele of ACVR1[R258G] in the mouse, Acvr1[R258G]FlEx/+, similar to that previously used to model the R206H mutation (Hatsell, Idone et al. 2015). Body-wide activation of the FOP allele in Acvr1[R258G]FlEx/+;Gt(ROSA26)Sor-CreERt2/+ adult mice resulted in progressive ossification, evident radiographically as early as 2 weeks after dosing with tamoxifen in a similar manner to that seen with the previously published Acvr1R206HFlex mouse. Detailed studies to determine whether this mutation has a different and more severe embryonic phenotype compared to R206H are ongoing. We have previously shown that HO resulting from R206H mutation is Activin A dependent and can be completely blocked with the administration of an Activin A blocking antibody. Other FOP causing mutations also render Acvr1 responsive to Activin A (Hino et al 2015) suggesting Activin A blockade would also be effective in inhibiting HO formation induced by these mutations. Here we show that HO generated by the R258G mutation is also Activin A dependent in this mouse model.
Disclosure
All authors are are employees of Regeneron Pharmaceuticals Inc., and hold stock in the company.

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P122

Congenital hyperinsulinism of infancy in a child with autosomal dominant hypocalcaemia type 1 due to an activating calcium sensing receptor mutation

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Background
Autosomal dominant hypocalcaemia (ADH) is caused by activating mutations of the calcium sensing receptor (CaSR). Symptomatology ranges from asymptomatic hypocalcaemia to paraesthesia, tetani, laryngospasm and seizures. This is the first report of congenital hyperinsulinism (CHI) in a child with ADH.
Presenting problem and clinical management
A female infant, born at term from non-consanguineous parents. She presented on D2 with persistent asymptomatic hypoglycaemia requiring 11mg/kg/min glucose. Investigations showed raised insulin and C-peptide, low beta-hydroxybutyrate and NEFA, consistent with CHI. She was started on diazoxide and chlorothiazide by D15. Diazoxide was stopped thrice, unsuccessfully, and she is currently, at the age of 15 months, on a dose of 2.5 mg/kg/day. On D4 she developed tonic-clonic seizures, with hypocalcemia and hypomagnesemia. She had undetectable PTH and high calcium/creatinine ratio, suggestive of ADH. Hypocalcemic seizures were difficult to control with high doses of alpha-calcidol, calcium and magnesium. At 11weeks of age she was started on treatment with subcutaneous continuous PTH via a Medtronic pump, after which seizures improved and calcium supplements were successfully stopped. From early age, she had difficulties in gaining weight, and had polyuria, raised urea and creatinine, hypokalemia and hyperaldosteronism, in line with a Bartter typeV, requiring potassium supplementation. Sequencing of CASR showed a de novo mutation c.2528C>A(Ala843Glu) previously described in ADH with Bartter Syndrome. Functional studies show constitutively active CaSR. No mutations in genes on the extended CHI panel were found. (KCNJ11, ABCC8, AKT2, GLUD1, GCK, GPC3, HADH, HNF4A, INSR, KDM6A, KMT2D, SCL16A1, CACNA1D, PMM2, TRMT10A, HNF1A).
Discussion
c.2528C>A(Ala843Glu)CaSR leads to severe ADH1 and can cause Bartter Syndrome typeV, likely due to the effect of constitutively active CaSR on the Na:K:2Clco-transporter and ROMK in the thick ascending limb of Henle's loop. No link between hyperinsulinism and ADH has been previously described. However, CaSR is expressed in the alpha and beta cells of the pancreas and CaSRNuf/Nuf mice that harbor an activating CaSR show hyperglycemia due to impaired beta-cell function and higher number of alpha-cells. We hypothesize that the active CaSR interferes with regulation of insulin secretion at young age, resulting in CHI, and at later age, results in beta-cell defects. Further work is required to understand the relation between CaSR, potassium transport and beta-cell function in ADH.
Disclosure
The authors declared no competing interests.

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P123

Odontochondrodysplasia in association with a TRIP11 mutation

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Background
Pathogenic mutations in thyroid hormone receptor interactor 11 (TRIP11) have previously been associated with achondrogenesis1A, a lethal autosomal recessive skeletal dysplasia. Recent findings have suggested that hypomorphic mutations of TRIP11 result in odontochondrodysplasia (ODCD), a rare syndrome associated with spondylometaphyseal dysplasia and dentinogenesis imperfecta.
Presenting problem
This is the case of a term female born to non-consanguineous parents with an unidentified skeletal dysplasia. Short bones were initially detected on a third trimester antenatal ultrasound. While her birth weight was 3 kg (25th–50th centile) by the age of 3.5 years her weight and height are less than the 0.4th centile while her OFC is above the 91st centile. She exhibits mesomelia, genu valgum, a small thoracic diameter with pectus carinatum and lumbar lordosis. She has hypermobile joints and flat feet. She has white sclera, dentinogenesis imperfecta but no history of fractures. Developmentally, she has a normal intellect and met her milestones appropriately apart from gross motor delay in walking at 2.5 years of age. Radiologically, she has evidence of congenital platyspondyly, vertebral coronal clefts, relatively long fibulae and valgus deformity of the femoral necks.
Clinical Management
The clinical diagnosis of ODCD was made in the first year of life through consultation with the European skeletal dysplasia network. Genetic screening for mutations in the achondrogenesis 3-gene panel confirmed a heterozygous mutation for the TRIP11 gene (c.1314 + 1G?A(;)3082C > T) in early 2019. Our index case receives ongoing multidisciplinary input from respiratory, dental and developmental paediatrics as well as routine bone health surveillance. Her family have been referred for genetic counselling in light of the postulated recessive nature of this condition.
Discussion
ODCD is a rare skeletal dysplasia which has only recently been ascribed to hypomorphic mutations of TRIP11 gene. TRIP11 is essential for endochondral ossification. Our case exhibits the dental changes characteristic of DI but no evidence of polycystic renal disease or obstructive hydrocephalus. This is the first case reported of ODCD due to a TRIP11 mutation in Ireland. This diagnosis will enable the family to link with other affected families and provide shared knowledge essential for surveillance and follow-up.
Disclosure
The authors declared no competing interests.

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P124

Heterozygous CDC73 mutation causing parathyroid adenoma in an adolescent girl presenting with mental health issues

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Background
Primary hyperparathyroidism (PH), whilst common in elderly populations, is much rarer in adolescents. Although up to 90% of cases are sporadic in nature, hereditary cases make up less than 10% of remaining causes. Multiple genetic causes and syndromes have been described in the literature including multiple endocrine neoplasia (MEN), familial hypocalciuric hypercalcemia and hyperparathyroidism-jaw tumour syndrome (HPT-JT).
Presenting problem
A 14-year-old girl with a past history of depression, chronic constipation, bony pains and self-harm was admitted from a Tier 4 CAMHS (Children and Adolescent Mental Health Service) unit following an overdose of fluoxetine. Investigations revealed hypercalcemia (adjusted calcium 3.66mmol/L), hypophosphatemia, vitamin D insufficiency and significantly elevated PTH at 82.9pmol/L (range 1.1–6.9 pmol/L) with increased urinary calcium excretion.
Clinical management
She was initially managed with intravenous fluids and furosemide. Due to persistent hypercalcemia, she was subsequently treated with bisphosphonates, cinacalcet and calcitonin. Her vitamin D levels where supplemented. Ultrasound and sestamibi scan revealed an enlarged parathyroid mass adjacent to the left upper pole of the thyroid gland. Pituitary function was normal as were x-rays of her hand, spine and ultrasound of her renal tract. The parathyroid adenoma was removed surgically. She was hypocalcaemic in the immediate post-operative period requiring calcium supplements. Her PTH levels normalised post surgery and improvement in her psychiatric symptoms was observed. Molecular genetic testing revealed a heterozygous mutation of CDC73. There was no significant family history, although her mother and sister will be screened.
Discussion
Psychiatirc symptoms including depression and self-harm are reconginsed features of hypercalcemia, particularly in patients with primary hyperparathyroidism. In these situations, some or all of their presenting symptoms can reflect parathyroid pathology not psychiatric. Baseline screening should be considered, including bone profile, to rule out organic pathology. Particularly in cases needing inpatient psychiatric admission or in patients with other symptoms suggestive of underlying calcium disorder. Mutations in CDC73 are associated with HPT-JT syndrome. It can lead to parathyroid tumours and ossified lesions of the jaw, renal tract and uterus. Early detection is important in surveillance and treatment of complications in addition to allowing genetic counselling for patients and family.
Disclosure
The authors declared no competing interests.

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P125

SCN8a mutations and osteoporosis. Is osteocyte dysfunction the cause or the consequence?

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Background
Mutations in the SCN8a gene, which encodes one of the most abundant voltage gated sodium channels; Nav1.6, has a strong association with epileptic encephalopathy type 13, ataxia, muscle atrophy and intellectual disability. Previous cases of pathological skeletal fractures in children with known SCN8a mutations have been published but the source of the related skeletal mechanism remains unclear.
Presenting problem
The proband presented at 15months of age to our service with a diagnosis of infantile epileptic encephalopathy due to a known SCN8a variant (c.4400T > G,Phe1467Cys). She was born at term following normal pregnancy to non-consanguineous Caucasian Irish parents. She developed jittery episodes postnatally which evolved into seizures unresponsive to phenobarbitone and clonazepam. She is currently managed on sodium valproate and topiramate. Fractures of the right femur, radius and left femur have been picked up on X-ray imaging precipitated by reduced limb movement following intractable seizure activity at 15 months and again at 20 months.
Clinical management
Biochemical markers of bone turnover were consistent with normal bone metabolism and mineralization. She was commenced on vitamin D supplementation due to her anti-epileptic medications. She proceeded to bone biopsy analysis. This showed increased osteoclast numbers and high osteocyte density with unmineralized peri-osteocytic areas suggestive of osteocyte dysfunction. Bisphosphonate treatment with Zoledronic acid was initiated at 21 months of age and there have been no further fractures despite further episodes of generalised seizure activity.
Discussion
Pathological fractures in intractable epilepsy are often attributed to trauma incurred during seizure activity, disuse osteoporosis secondary to neurological or the result of multiple anti-epileptic medications. We postulate that the cause is her underlying mutation resulting in osteocyte dysfunction. Case reports of children with severe juvenile osteoporosis affected by this mutation have been published but have not reported bone histomorphometry. A homozygous SCN8A null mouse model has shown increased osteoclastogenesis suggesting the involvement of the Nav1.6 voltage gated sodium channel in skeletal turnover. Treatment with bisphosphonates has led to successful fracture prevention. We advocate that individuals with SCN8a mutations should receive surveillance for skeletal complications and may benefit from initiation of bisphosphonate treatment.
Disclosure
The authors declared no competing interests.

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P126

Anemia - novel clinically significant finding during intravenous pamidronate therapy of children diagnosed with osteogenesis imperfecta

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Osteogenesis imperfecta (OI) is a rare genetic disorder characterized by fragile bones susceptible to fractures. No definite cure for OI exists. Bisphosphonates, although not implicitly recommended in children due to deficient efficacy and safety data, have been administered off-label to OI patients for over 20 years. Short-term adverse effects of intravenously administered bisphosphonates are generally mild. Although anemia is a known side effect of bisphosphonates in adults, thus far no study has evaluated or described this potential adverse reaction to intravenous pamidronate in children with OI. The aim of the study was to evaluate short-term adverse effects resulting from intravenous pamidronate administration in children with OI, with special regard to hematologic parameters. We retrospectively analyzed clinical data from 313 pamidronate administrations in 60 pediatric patients diagnosed with OI, treated at Department of Pediatric Propedeutics and Metabolic Bone Diseases, Medical University of Lodz. Median age across all analyzed treatment cycles was 6 years, with the youngest child being 11 days old and the oldest 17.8 years old at the moment of pamidronate administration. Fever, flu-like syndrome on first infusion and mild hypocalcemia occurred most frequently during the first infusion. Most children experienced changes in blood morphology, with a significant hemoglobin level reduction (median 12.8 g/dL before vs 12.1 g/dL after administration; $P<0.01$) consistent with a decrease of red blood cell count (median 4.7×106/mL before vs 4.5×106/mL after administration; $P<0.01$). In 64 out of 313 analyzed cycles, children experienced anemia following pamidronate infusion. Intravenous pamidronate administration is therefore associated with lowering of red blood cell parameters in children with osteogenesis imperfecta. This effect is currently underappreciated and should be taken into account by physicians administering pamidronate off-label to OI patients. The precise mechanism and clinical relevance of these findings warrant further investigations.

Disclosure

The authors declared no competing interests.

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P127

Burosumab therapy in pediatric patients with X-linked hypophosphatemia improves body composition

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Objective

Burosumab, a recombinant human monoclonal antibody that inhibits FGF23, was approved by the FDA in April, 2018 for the treatment of X-linked hypophosphatemia (XLH) in children and adults. XLH pediatric patients are typically affected with lower extremity deformities, short stature, bone pain, and limited physical activity. Burosumab is superior to conventional therapy in normalizing blood phosphate levels, thereby healing rickets, decreasing leg bowing, and reducing pain. Data on the impact of burosumab on pediatric patients' growth are limited and data on their body composition are lacking altogether.

Methods

In May 2018, 6 XLH patients (2 males), age range 4–11.5 years, were started on subcutaneous burosumab therapy in our tertiary medical center. Burosumab was administered every 2 weeks, and dose-adjusted (between 0.4–1.9mg/kg) to achieve a serum phosphorus level at the low end of the normal range. Oral phosphate supplement and calcitriol were discontinued before starting burosumab. Anthropometric and body composition measurements, i.e., body fat percentage and distribution, muscle mass and distribution [bioelectrical impedance scale in children >5 years old] were assessed at treatment initiation, at 3 and 6 months.

Results

Growth velocity of burosumab-treated patients increased from baseline to 3 and 6 months: 5.1 ± 0.7 cm/year, 9.0 ± 1.9 cm/year, and 7.8 ± 1.5 cm/year. Mean height z-scores gradually increased, while mean body mass index z-scores gradually decreased (-1.87 ± 0.74 SDS, -1.74 ± 0.72 SDS, and -1.63 ± 0.64 SDS; 1.17 ± 0.55SDS, 1.06 ± 0.44 SDS, and 1.03 ± 0.48 SDS from baseline to 3 and 6 months, respectively). Body composition of 4 patients (2 males; >5 years) showed gradual reduction in body fat percentage (25.7 ± 3.3, 25.2 ± 2.6, and 23.9 ± 3.0), with increased muscle mass that was greater in the lower limbs (right leg: 3.1 ± 1.3, 3.2 ± 1.3, and 3.4 ± 1.4; left leg:3.0 ± 1.3; 3.2 ± 1.3, and 3.3 ± 1.3). All the patients reported decreased pain and increased ability to engage in physical activity. Adverse events were local and mild.

Discussion

We demonstrated a new and not yet recognized important beneficial effect of burosumab therapy on body composition of treated children: decreased fat percentage with simultaneous increased muscle mass, especially in the lower limbs. Burosumab cures rachitic bone changes, reduces pain, and improves patients' physical capabilities. Studies with long-term follow-up are needed for further examination of burosumab's impact on body composition and its metabolic implications.

Disclosure

The authors declared no competing interests.

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P128

Growth hormone effect on bone mineral density in a girl with osteogenesis imperfecta – a case presentation

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Background

Osteogenesis imperfecta (OI) is characterized by bone fragility, resulting in low-energy fractures. Other features are compromised growth, blue sclerae, dental, cardiac and hearing abnormalities.

Presenting problem

A girl with OI, hypothyroidism and growth hormone (GH) deficiency is presented. She was born at 32 weeks [birth weight: 1890 gr, length: 44 cm]. Her mother had OI and thyroid nodules. Both were found with heterozygous mutation in the COL1A1 gene (c.2453dupG, pAla819fsX2). She presented at 5.7 yrs of age for growth failure and reported no fractures. She was on L-thyroxin due to primary hypothyroidism. On examination, her height was 99.7 cm (-2.9 SDS), weight: 15 kg (-2.25 SDS) and she had blue sclerae and hyperextensible joints. Baseline investigations [complete blood count, liver, renal and thyroid function and basic bone profile] were normal. IGF1 was low (88 ng/ml) and peak GH secretion was low at glucagon and clonidine stimulation tests (<10 ng/ml). Her bone age was delayed by two years and pituitary MRI was normal.

Clinical management

Replacement therapy with rhGH was started. She sustained a low-energy fracture at age 6.3 years and reported occasional, mild lumbar pain. A lateral spine Xray did not reveal vertebral fractures. Lumbar spine bone mineral density (BMD) was low for her age and sex, adjusted for height (Z-score $=-3.2$); so was the subcranial total body scan, with BMD Z-score $=-2.6$, at six months after initiation of therapy. After two years of rhGH treatment, her height was 117.8 cm (-2.2 SDS) and the follow up BMD Z-scores of the lumbar spine and total body scan were improved (-2 and -1.3, respectively).

Discussion

GH has a positive effect on bone growth and turnover by stimulating osteoblasts, collagen synthesis and longitudinal bone growth. Sillence *et al.* showed positive effects of GH on height, skeletal volume and BMD, and infer that it may be beneficial for these group of patients. Despite the lack of robust evidence for the use of GH in OI, our case illustrates the potential for skeletal improvement in OI patients with mild phenotype and confirmed GH deficiency and highlights the importance of investigating short stature in these patients thoroughly.

Disclosure

The authors declared no competing interests.

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P129

A smartphone-based survey of frequency and severity of adverse effects following bisphosphonate therapy in a Tertiary Paediatric Centre

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Objectives
The primary objective of this project was to determine the nature and timing of perceived early adverse effects associated with bisphosphonate therapy. Additional information was sought on how this affected the child and family, to determine if changes should be made to local guidelines.
Methods
A Smartphone-based text message survey was sent to parents of patients receiving intravenous bisphosphonate therapy for primary and secondary osteoporosis. Patients in our unit were routinely admitted for 24 hours for their first infusion, but not subsequent ones. The survey was designed to assess the nature, severity and impact of adverse effects at three defined timepoints: the day of, three days after, and five days after bisphosphonate administration. Surveys were received by text message with a link to the online questionnaire.
Results
The day one response rate was 90% from twenty surveys. Day three and five response rates were 80% and 65% respectively. The majority of adverse effects occurred more than 24 hours after bisphosphonate administration. On day one, 16% of children reported being unwell immediately following infusion. 62% of respondents to the day three survey reported being unwell on day two or three following treatment. The highest frequency of adverse events was reported on the day five survey, with 69% of patients reporting adverse effects on days four or five. The most commonly reported symptom was fever (50%), with generalised pains and lethargy also commonly mentioned. $>90\%$ who experienced adverse effects required time off school and $>60\%$ visited hospital for further assessment and treatment.
Conclusion
This novel text-based survey had a good response rate and highlights the known adverse effects associated with bisphosphonate therapy. Valuable information about timing of symptoms has stimulated two main changes in clinical practice locally:

1. Patients are no longer admitted for their first bisphosphonate infusion, as the majority of adverse effects did not occur in the first 24 hours after administration.
2. Parents are given more detailed information about what to expect with regard to potential adverse effects and subsequent management, to reduce associated hospital visits and disruption to daily routines.

Disclosure
The authors declared no competing interests.

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P130

Off label uses of pamidronate in rare pediatric bone diseases (Jansen's Metaphyseal Chondrodysplasia and Generalized Arterial Calcification of Infancy): A four year perspective

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Background
Pamidronate is FDA approved only in adults. It is frequently used off-label in the treatment of pediatric bone diseases, such as osteogenesis imperfecta, juvenile osteoporosis, and osteopenia in nonambulatory patients with cerebral palsy. The use of pamidronate in these conditions is relatively common, but there may be more to be understood about its role in other rare pediatric bone diseases.
Presenting problem
Jansen's Metaphyseal Chondrodysplasia (JMC) is an ultra-rare, autosomal-dominant, skeletal dysplasia caused by activating mutations in the PTH/PTHRP receptor PTHR1. It is characterized by severe hypercalcemia, hypophosphatemia, decreased TRP, normal/elevated levels of 1,25-dihydroxyvitamin D3, and very low levels of PTH or PTH-related peptide (PTHrP). While bisphosphonates are an established treatment of hypercalcemia for other conditions, its use in JMC is more uncertain. However, it is posited that bisphosphonates may reduce hypercalcemia, hypercalciuria, nephrocalcinosis, and decrease bone turnover in patients with JMC. Generalized arterial calcification of infancy (GACI) is an ultra-rare, autosomal recessive disorder with high infantile mortality, characterized by calcifications of large and medium vessels, leading to arterial stenosis and decreased vascular elasticity. Inactivating mutations in the ENPP gene lead to decreased levels of inorganic pyrophosphate, an inhibitor of hydroxyapatite-crystal deposition in blood vessels. Less commonly, mutations in ABCC6 lead to ectopic tissue calcification in the skin and arterial blood vessels, but the mechanism is unknown. In patients with GACI, it is posited that bisphosphonates, which are analogs of inorganic pyrophosphate, interfere with hydroxyapatite crystal formation, inhibit further calcium deposition of existing lesions, and decrease bone turnover.
Clinical management
One patient with JMC and three patients with GACI were treated with IV pamidronate, initial dose of 0.5 mg/kg per dose $\times 3$ consecutive days, then 1–1.5 mg/kg per dose at varying intervals. The patient with JMC had control of his hypercalcemia, improved mobility, and decreased pain. Patients with GACI were simultaneously treated with oral acetazolamide, and had normalization of serum calcium, and reduction or complete resolution of their vascular calcification.
Discussion
Because these disorders are ultra-rare, it is unlikely that randomized, controlled trials of bisphosphonate therapy will be undertaken, which makes case reports of efficacy of this treatment in these disorders vitally important.
Disclosure
The authors declared no competing interests.

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P131

Use of intravenous pamidronate in pediatric acute lymphoblastic leukemia patients with osteonecrosis (ON) results in reduced pain and improved radiologic outcome of ON lesions: Long- term follow-up over 15-years

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Background
Osteonecrosis (ON) has emerged as a debilitating complication of acute pediatric lymphoblastic leukemia (pALL), with severe pain and poor functional outcome. ON affecting weight bearing joints may eventually need arthroplasty, with large juxta-articular lesions being at highest risk. Intravenous Pamidronate (IV-PAM) is postulated to reduce pain and prevent joint collapse in ON.
Objective
To study if IV-PAM was effective in 1) preventing joint ON progression and need for surgical intervention and in 2) reducing ON related pain in pALL.
Methods
All consecutive pALL patients (0–18 years) who developed bone pain were assessed for ON with a whole body MRI (WB-MRI). Patients with confirmed ON received two 9-month courses (induction and maintenance) of once/monthly IV-PAM (first dose 0.5 mg/kg; all others 1 mg/kg per dose; maximum dose 11.5 mg/mg per year). Visual analogue score for pain (VAS), with '0' being 'no-pain' and '10' being 'the worst possible pain' was administered at baseline, 3, 6 and 12 months and yearly. The radiologic outcome was assessed by serial WB-MRIs.
Results
Out of 40 pALL patients referred for assessment of bone pain, all had osteoporosis and 24/40 had ON (9F:15M). ON was multisite in 24/24; with 10/24 having upper limb and 20/24 having lower limb lesions. ON affected 26 large joints (shoulders [10], hips [4] and knees [12]). Four hips, knees and ankles had $>50\%$ articular surface involvement by ON. The mean duration of follow-up was 7 (range 3–15) years. None of the large joint ON required surgery: two femoral heads developed minor collapse, while other ON lesions remained stable or resolved. The mean pain VAS pre-pamidronate was 8.5/10 (range 8–10/10; 0.1/10 (range 0–1/10) at 6 months, and unchanged at 0. 08/10 (range 0–1/10) at 12 months and at final follow-up.
Conclusions
Our results suggest that IV-PAM is effective in controlling ON related pain and may prevent joint ON progression and orthopedic surgery.
Disclosure
The authors declared no competing interests.

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P132

A prospective study of 17 consecutive pediatric patients with chronic non-bacterial osteomyelitis treated with intravenous pamidronate over a 15 year period at a single center reveals excellent clinical and radiologic outcome initially and after flare

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Objectives
To describe a prospective series of pediatric CNO (pCNO) patients treated with IV-Pamidronate (IV-PAM) regarding effect on 1) pain, 2) Whole Body Magnetic Resonance Imaging (WBMRI) documented inflammation; 3) Spinal CNO and 4) bone turnover.
Methods
All pCNO patients (<18 years at diagnosis) with WBMRI confirmed active CNO who were treated with IV-PAM between 2003–2018. IV-PAM: First dose 0.5 mg/kg; subsequently 1 mg/kg (max dose 60 mg), administered once monthly x 9 (max) initially and after WBMRI confirmed flare. Pain: Visual analogue scale for pain (VAS) with '0' indicating no pain and '10' maximum pain was administered at baseline, at each IV-PAM, and at suspected flare. Imaging: WBMRI before 1st IV-PAM, at 6 and 12 months, at suspected flare and after retreatment. Complete resolution (CR) was defined as >95% resolution of abnormal signal on WBMRI. UNtx/Cr was collected at baseline and monthly.
Results
17 patients (9F, 8M) were included with median [range] follow-up 9.2[1–15] years. The median [range] age at CNO diagnosis was 10.3[4–15] years, and at first IV-PAM 11.6[4–20] years. CNO was unifocal in 6/17; spinal in 4/17 (baseline vertebral fractures in 2/4) and multifocal in 7/17. VAS was uniformly 10/10 at baseline, and decreased to 0–1/10 after 1st IV-PAM. All patients reached CR at 6 months. No flares occurred in 5/17; 12/17 relapsed at 9–36 months and 11/17 received 2nd course of IV-PAM (1–9 doses). With flare, VAS ranged from 4–9/10 and decreased to 0–3/10 after 1st IV-PAM. On final WBMRI, 12/17 (70%) had CR and 5/17 (30%) stable increased signal but no clinical symptoms. No new spinal fractures developed. UNtx/Cr decreased after 1st IV-PAM and no flares occurred while UNtx/Cr remained suppressed. Arthritis developed in 3/17. At last follow-up, 10/17 (59%) patients required no medications, 4/17 (24%) required prn Naproxen and 3/17 (18%) DMARDS for arthritis.
Conclusion
Long-term follow-up confirms that initial beneficial effects of IV-PAM are sustained with flares with no further spinal fractures. No flares occurred while UNTX/Cr remained suppressed, suggesting a role of osteoclasts in CNO. Further multicenter studies are required to define the long-term clinical and imaging response to IV-PAM.
Disclosure
The authors declared no competing interests.

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P133

Losartan reduces circulating TGFb and CTX and increases vertebral bone mass in the OIM mouse

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Objectives
Losartan is an angiotensin II receptor type 1 (AT1) antagonist. Losartan reduces circulating TGFb concentrations in a variety of myopathic models. We hypothesised that losartan administration to the murine osteogenesis imperfecta model OIM would result in lower circulating TGFb and CTX (bone resorption marker) and increase bone mass.
Methods
All procedures were approved by UConn Health Institutional Animal Care and Use Committee and performed in an AAALACi accredited facility. OIM mice were obtained from Jackson Labs (Bar Harbor, ME) on a mixed background (B6C3Fe a/a-Col1a2oim/J) for Study 1 and then rederived onto a C57BL6 background for Study 2. OIM mice were administered losartan via their drinking water at concentrations of 0 g/l, 0.6 g/l and 1.2 g/l for 4-weeks in study 1 or 0 g/l or 0.6 g/l for 8-weeks in study 2. Following termination, Serum TGFb and CTX were measured by ELISA and bone volume/integrity was measured in vertebral bodies by uCT. Data reported as mean (S.D.).
Results
In Study 1, 4 weeks' losartan at 0.6 g/l, but not 1.2 g/l, was associated with a significant reduction in TGFb (ng/ml): losartan 0 g/l, 79.2 (14.6); 0.6 g/l, 60.0 (18.6) $P=0.0440$ vs 0 g/l; 1.2 g/l, 82.1 (18.7); and in CTX (ng/ml): Losartan 0 g/l, 275.9 (100.2); 0.6 g/l, 157.2 (128.2) $P=0.0205$ vs 0 g/l; 1.2 g/l, 263.1 (80.7). In Study 2, 8 weeks' losartan treatment at 0.6 g/l vs 0 g/l was associated with significant differences in L3 vertebral body BV/TV%; 63.7 (40.0) vs 10.0 (2.0) $P=0.0215$; Tb. N. 0.019 (0.003) vs 0.014 (0.003) $P=0.0158$; Tb. Sp. 17.6 (17.4) vs 46.4 (5.3) $P=0.0085$; and Tb. Th 33.1 (20.8) vs 6.9 (0.2) $P=0.0278$. CTX and TGFb measured at 8 weeks were not significantly different between treated and control mice.
Conclusions
Losartan 0.6 g/l reduced bone turnover and TGFb at 4 weeks and increased vertebral trabecular bone mass at 8 weeks. The lack of difference in CTX and TGFb at 8 weeks suggests earlier reductions in bone turnover, resulting in increased retention of trabecular bone, that are carried through to 8 weeks of age when turnover is intrinsically lower in both treated and untreated animals. Further studies are needed to clarify the biological mechanisms and pathways involved.
Disclosure
NJB consults for Alexion, Mereo, UCB and Amgen, and receives grant support for clinical studies from Alexion and Amgen.

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P134

First report of skin reaction with Zoledronic Acid

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Adverse reactions to bisphosphonates are common and thus, most of them are predictable side effects to the drug. Allergic reactions or skin reactions of any type or severity associated with bisphosphonates have been scarcely described in the literature. Allergic and skin reactions to bisphosphonates have been estimated to occur in less than 1% of patients. The mechanism of these reactions is unknown, although it is presumed to be IgE mediated. All of the bisphosphonates share a similar chemical structure suggesting susceptibility to cross reactivity for immunologically mediated reactions. We report the case of a 5-year-old female patient with Rett syndrome who had a very low bone mass (Z score below -2SD) and experienced a non-traumatic femoral fracture. Spine X-rays showed a vertebral fracture (genant 1). Laboratory measurements were in the normal. It was decided to treat her with bisphosphonates and she received a first intravenous dose of Zoledronic acid (ZOL) with no side effects. However, immediately after the second dose of zoledronic acid infusion, she developed an anaphylactic reaction with major urticarial eruption. She had no previous history of allergic symptoms after tacking any medication. IgE mediation of the reaction was suggested. Prick and intradermal skin testing to pamidronate and zoledronic acid at different concentrations were performed and confirmed by a positive immediate skin test a IgE mediated allergy to zoledronic acid and lack of skin response to pamidronate. A positive skin test response to a non-irritant concentration of a specific bisphosphonate suggested the formation of IgE antibody to that bisphosphonate. She was then treated by IV pamidronate and never presented any skin reaction after then. To our knowledge, this is the first case of skin reaction reported with zoledronic acid.
Disclosure
The authors declared no competing interests.

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P135

Oral ibandronate therapy in patients with osteogenesis imperfecta

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Background
Treatment with orally administered ibandronate is an effective way to increase bone mineral density (BMD) and reduce fracture rate in post-menopausal women and in men with osteoporosis. There are only very few reports concerning ibandronate therapy in children/adolescents, and in patients with osteogenesis imperfecta (OI), as bisphosphonates are off-label drugs in pediatrics.

Case presentation
We present two patients with OI type I (14 year old boy and 11 year old girl, both with history of prevalent low-energy-trauma fractures) where once-monthly oral ibandronate (150 mg tablets) plus cholecalciferol 1000 IU/day and calcium 1000 mg/day increased spinal BMD (DXA-Lunar) after one year of therapy by 41% (from Z-score −5.1 s.d. to −2.9 s.d.) and 31% (Z-score −3.0 s.d. to −1.8 s.d.), respectively, without any occurrence of new fractures or adverse reactions. There were no alterations in the laboratory parameters that were assessed every three months and also no dental problems, neither gastrointestinal irritation. The treatment is still ongoing.
Conclusion
Once-monthly oral ibandronate increased BMD and most probably improved bone quality in pediatric patients with OI.
What is new.
- One year treatment with once-monthly oral ibandronate resulted in an impressive increase in spinal BMD in individual patients with OI.
- No new fractures occurred.
- The oral ibandronate therapy was well tolerated without any adverse events or adverse reactions.

Disclosure
The authors declared no competing interests.
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P136

Intravenous bisphosphonate treatment in severe infantile hypercalcemia associated with Williams Syndrome
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Background
Infantile hypercalcemia occurs in ∼15% of patients with Williams Syndrome (WS) and is typically mild. Severe hypercalcemia has been reported in infants/toddlers with WS, requiring treatment with intravenous (IV) saline hydration, furosemide, calcitonin, calcium and vitamin D restriction, and in some cases IV bisphosphonates.
Presenting problem
Three cases of infants with WS age 9–13 months presented with severe hypercalcemia, failure to thrive, increasing irritability, lethargy, regression of developmental milestones, and hypotonia. All patients had dysmorphic features characteristic of WS with cardiac defects (supravalvular aortic stenosis in 2 and pulmonary stenosis in 1). Initial lab/imaging studies revealed marked hypercalcemia, with serum calcium ranging from 17.2–21.7 mg/dl [4.3–5.4 mmol/l] (normal 8–10.5 mg/dl [2.0–2.6 mmol/l]), low serum phosphorus, suppressed parathyroid hormone, normal 25-hydroxy vitamin D, elevated BUN and creatinine, hypercalciuria, and bilateral medullary nephrocalcinosis on renal ultrasound.
Clinical management
Conventional therapy with saline hydration, furosemide and subcutaneous calcitonin decreased serum calcium levels to some degree, but failed to normalize the calcium levels. Due to persistent hypercalcemia, 2 doses of IV pamidronate (PAM) were given in Patients A and B. Follow up calcium levels have been normal or mildly elevated (10.8 mg/dl [2.7 mmol/l]) in Patient A. In Patient B, rebound hypercalcemia was noted within a month of PAM prompting treatment with zoledronic acid (ZA) at 0.05 mg/kg per dose, with subsequent normocalcemia throughout 2.5 years post-therapy. In Patient C (initial serum calcium of 17.8 mg/dl [4.4 mmol/l]), IV ZA at 0.025 mg/kg per dose was administered after inadequate response to conventional therapy. Calcium levels normalized within 8 hours after ZA, with stable clinical course and shortest hospital stay. Clinical improvement in all areas including general well-being, muscle tone, growth and development was noted in all three patients after hypercalcemia was corrected.
Discussion
Severe hypercalcemia, which requires aggressive therapy, can occur in infants with WS, leading to significant complications including failure to thrive, developmental delay, acute kidney injury and nephrocalcinosis. We report the first successful use of ZA in infants with WS that resulted in rapid and sustained normalization of hypercalcemia. Treatment with ZA should be considered in WS with severe life-threatening hypercalcemia after failed conventional therapy.
Disclosure
The authors declared no competing interests.
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P137

Reversion to pamidronate after switch to zoledronic acid in children with bone disease
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Objectives
From late 2015 a new protocol for zoledronic acid was adopted in our centre. This led to many children changing from pamidronate (PAM) to zoledronic acid (ZA) treatment. In a minority of cases the children and/or their families felt strongly that they wanted to change back to PAM. We present the characteristics of that minority and how bone turnover markers (BTMs) and bone mineral densities (BMD) changed whilst on ZA.
Method
From Nov 2016 to Oct 2018, 9/29 children changed back to PAM from ZA. We retrospectively reviewed their clinical records.
Results
Diagnoses were: osteogenesis imperfecta x4; other osteoporosis x2; Ehlers Danlos x1; fibrous dyplasia x1; Duchenne muscular dystrophy x1. Median duration on PAM pre-ZA was 2.3 yrs (1.1–7.7 yrs). Median period of time on ZA was 0.8 yrs (0.5–2.0 yrs). Median number of doses before reversion to PAM was 2 (1–4); 8/9 were on 6 monthly ZA. Median age at time changed back to PAM 13.7 yrs (3.6–17.9 yrs). Reason for reversion in vast majority (7/9) was less effective pain relief ± more fatigue. Others reported deterioration in sleep and mobility or increased appetite. Whilst on ZA: median annualised % change in serum ALP ($n=8$) −1.5% (−120% to +61%); median annualised % change in urine NTx ($n=8$) −14% (−82% to +243%); and median annualised % change in L2-4 BMD ($n=8$) 7% (+1% to +37%). Unsurprisingly, the longer an individual had been on PAM the smaller the % change in BMD on ZA and, correspondingly, the younger the individual the greater the reduction in NTx.
Conclusion
Whilst there was a broadly consistent view expressed by the respective children and parents that ZA was less effective at managing symptoms, there was no corresponding consistency of change in BTMs or BMD. Our clear impression is that there are some children who appear to obtain greater symptomatic benefit from PAM compared to ZA and vice versa. The biological basis for this is unclear. Over time, our practice has evolved and we are now more likely to offer 3 monthly ZA even to older children in whom 6 monthly ZA fails to control symptoms.
Disclosure
Nick Bishop: Consults for Alexion, Mereo, UCB and Amgen, and receives grant support for clinical studies from Alexion and Amgen. Paul Arundel: Research grant/honoraria/ expenses – Alexion and Kyowa Kirin. Expenses – BioMarin.
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P138

How early is early enough – Bisphosphonate treatment in Osteogenesis imperfecta
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Objective
Osteogenesis imperfecta is characterized by hereditary skeletal fragility. Bisphosphonates are the first line medical treatment in moderate and severe OI types III/IV. There is no consensus regarding treatment beginning and treatment regimen in the first years. Objective of the presented project was the evaluation of the therapeutic effect of 1 year of bisphosphonate treatment (BP; neridronate i.v. 2 mg/kg body weight every 3 months) on vertebral shape and mobility in children with severe OI.
Methods
Matched pair analysis of 12 children with OI depending on time of initiation of bisphosphonate treatment (early starters 0–3 months; late starters 3–5 months). Areal Bone mineral density (BMD) of the lumbar spine (L2-L4) was assessed via DXA (GE Lunar iDXA). Vertebral shape was assessed by x-ray of the lateral spine (Morphometry score 'Körber'). Mobility was analysed by age when children reached motor milestones.
Results
Early starters ($n=6$, 4 females; OI type III $n=4$; OI IV $n=2$; age at start of BP treatment 0.65 ± 0.35 months) and late starters ($n=6$; 3 females; OI type III $n=3$; OI IV $n=3$; age at start of BP 3.8 ± 1.7 months) presented with a reduced mean lumbar BMD at start of treatment and after one year (early starters: 0.230 g/cm^2 vs 0.244 g/cm^2; late starters 0.131 g/cm^2 vs 0.236 g/cm^2). Vertebral morphometry

score changed from 1 to 24.8 and from 57.25 to 53.8 demonstrating a much more severely affected spine in the late starters. Motor function assessment revealed 'pulling to stand' with 13.6 months vs 15.0 months and 'first supported steps' with 17.0 vs 22.5 months.

Conclusion

Patients starting during the newborn period with i.v. neridronate treatment showed less deterioration of vertebral shape and tended to have a better motor function development than children starting at the mean age of 3.8 months. Therefore one can assume that an early antiresorptive treatment might be beneficial for the development of the affected children. Further trials are needed to outweigh risk and benefit especially regarding the long term course of the patients.

Disclosure

The authors declared no competing interests.

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P139

Growth hormone therapy in a child with severe short stature due to Miller-McKusick-Malvaux (3M) syndrome-2

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Background

3M syndrome is a primordial growth disorder caused by mutations in CUL7, OBSL1 or CCDC8. Affected individuals have severe short stature for which growth hormone (GH) therapy may have a role[1]. We present a 10-year-old girl from Sri Lanka with 3M syndrome-2 due to a mutation in OBSL1 gene, with good short-term response to growth hormone therapy.

Presenting Problem

The only child of second-degree consanguineous parents, both themselves children of second cousin marriages presented with severe short stature. She was born at 35 weeks of gestation with a birth length of 43 cm (<3rd centile), birth weight of 2.2 kg (10th centile) and head circumference of 33 cm (50th–90th centile). At 9 years of age her height was −5.5s.d., well below the mid-parental height range, and height velocity was 3 cm/y. She had features suggestive of 3M syndrome including upturned fleshy tipped nose, frontal bossing, triangular face, prominent heels, short chest and lumbar lordosis with mild scoliosis.

Clinical management

On investigation, basic biochemistry, Insulin-like Growth Factor-1 (IGF-1), stimulated peak growth hormone (GH) level, karyotype and mucopolysaccharidosis screening test results were normal. 3M syndrome was suspected, and genetic testing identified a homozygous splice site mutation in the Obscurin-like protein 1 (OBSL1) gene (c.2134+1G>A (chr2:220431551), associated with 3M syndrome[2]. Both parents were heterozygous for the same mutation. After counselling, she was commenced on GH therapy (5 mg/m^2 per week). In the first 6 months of therapy her HV increased to 4.8 cm/year, and height improved by +0.6 s.d. As IGF-1 level was within normal range, GH dose was increased to 5.5 mg/m^2 per day. Height gain and serum IGF-1 levels will be monitored regularly.

Discussion

This Sri-Lankan girl with 3M syndrome-2 due to OBSL1 gene mutation showed a reasonable short-term response to growth hormone therapy with height s.d. score improving from −5.5s.d. to −4.9s.d. after 6 months of therapy.

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Disclosure

The authors declared no competing interests.

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P140

Safety and effectiveness of stoss therapy in children

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Objectives

Pediatric vitamin D (25-hydroxyvitamin D - 25OHD) deficiency can lead to nutritional rickets and extra-skeletal complications. Compliance with daily therapy can be difficult, making high dose, short-term vitamin D (stoss) therapy attractive to correct vitamin D deficiency. We compared the effectiveness and safety of standard versus stoss therapy in treating childhood 25OHD deficiency.

Study design

Children aged 2–16 years with 25OHD <50 nmol/l were randomized to either standard (5,000 IUdaily for 80 days) or stoss (100,000 IU weekly for 4 weeks) cholecalciferol. Participants underwent evaluation of effectiveness and safety. 25OHD, random spot calcium: creatinine ratio (Ca:Cr) and compliance were measured at 12 weeks.

Results

151 children were enrolled in the study (68 standard and 83 stoss), median age 9 years (IQR: 6–12 years). Baseline 25OHD levels were 26 nmol/L (IQR: 19–35 nmol/l) and 32 nmol/l (IQR: 24–39 nmol/l) in the standard and stoss groups respectively. At 12 weeks, the median 25OHD level was significantly greater in the standard vs stoss group (81 vs 67 nmol/l; $P=0.005$), however, >80% of participants in both groups achieved sufficiency (25OHD>50 nmol/l) and had normal urinary Ca:Cr, with no significant difference seen between groups. Compliance was similar in the two groups.

Conclusion

Compared to stoss, standard therapy achieved higher 25OHD levels at 12 weeks; however, there were a similar number of participants with 25OHD sufficiency and safety. Unlike other studies, simplifying the treatment regimen did not improve compliance. These results support stoss therapy as an effective and safe alternative therapy for the treatment of pediatric vitamin D deficiency.

Disclosure

The authors declared no competing interests.

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P141

Hypercalcaemia and osteonecrosis of the jaw in association with denosumab use in the paediatric population

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Background

Denosumab (DMAB) is used in adults for the treatment of osteoporosis, giant cell tumour of bone, and cancer metastases. There are little data on paediatric use with clinical decision making reliant on adult data and clinical experience.

Presenting problem

We have treated 33 children with DMAB: Perthes disease ($n=9$), avascular necrosis ($n=17$), osteoporosis ($n=1$), aneurysmal bone cyst ($n=4$) and giant cell tumour ($n=2$). Treatment protocols have varied between conditions and over time with growing clinical experience. There have been five cases of hypercalcaemia, and one case of osteonecrosis of the jaw.

Patient 1

11-year-old female with Perthes disease (PD) treated with DMAB (1 mg/kg) 12 weekly, incidental finding of serum calcium 3.29 mmol/l before 4th dose of DMAB.

Patient 2

16-year-old male with avascular necrosis treated with DMAB (1 mg/kg) 12 weekly for 12 months followed by oral risedronate. Nausea and vomiting 3 weeks after stopping DMAB. Serum calcium 3.70 mmol/l.

Patient 3

10-year-old male with PD treated with 8 weekly DMAB (1 mg/kg) for 12 months followed by two doses of zoledronic acid (ZA). 12 weeks post DMAB, 4 weeks after first ZA, incidental finding of serum calcium 3.61 mmol/l.

Patient 4

15-year-old male with giant cell tumour of maxilla, treated with 4 weekly DMAB (1 mg/kg) for 18 months. 8 weeks post DMAB, 4 weeks after first ZA, incidental finding of serum calcium 3.87 mmol/l.

Patient 5
14-year-old male with an aneurysmal bone cyst of 3rd cervical vertebra. Treated with 4 weekly DMAB (60 mg) for 18 months, followed by two doses of ZA. Spontaneous osteonecrosis of the mandible after 18 months of DMAB therapy. Symptomatic hypercalcaemia 3 months post final ZA (6 months post final DMAB). Serum calcium 3.60 mmol/l.
Clinical management
Hypercalcaemia treated with intravenous rehydration and ZA without sequalae. Osteonecrosis of the jaw healing spontaneously.
Discussion
DMAB is a potent inhibitor of bone resorption, leading to excessive metaphyseal bone retention. Its potent action has the potential to improve outcome in paediatric bone disorders, but the optimal regimen to prevent complications is still to be determined. Our DMAB protocol continues to be revised to minimize hypercalcaemia risk.
Disclosure
The authors declared no competing interests.
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P142

Protocol: a randomized trial of zoledronate in children with cerebral palsy

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Objectives
Low bone mineral density is highly prevalent in non-ambulant cerebral palsy and is associated with a high risk of fractures. In most cases these fractures occur with no or minimal trauma. Primary and secondary fracture prevention strategies differ between sites and countries. In order to inform these strategies we intend to complete a trial of Zoledronate in children with Cerebral Palsy. We hypothesize that Zoledronate treatment significantly increases bone mineral density after 1 year compared with placebo.
Methods
We plan to include 52 children aged 5 to 17 years with non-ambulant Cerebral Palsy in a randomized controlled trial. Each child will receive 2 double blinded treatments of intravenous Zoledronate or placebo at a 6-month interval. The first dose is 0.025 mg/kg, the second dose is 0.050 mg/kg. The primary endpoint is the change in bone mineral density after 12 months as measured by Dual-energy X-ray Absorptiometry. We will use 3 regions of the distal femur as the primary site of measure.
Results
15 children have been included since October 2017. No serious adverse events have ocurred. More sites have been recruited and now 5 sites are including patients. Inclusion will continue until the end of 2019. Results are expected in 2021.
Conclusion
This study will add knowledge on the effect of Zoledronate in children with Cerebral Palsy and strengthen the fracture prevention strategies. The results may thus improve the quality of life of children with non-ambulant Cerebral Palsy. Further, health care spending on fracture management may be reduced.
Disclosure
The authors declared no competing interests.
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P143

Intermittent bi-daily sub-cutaneous teriparatide infusion in children with hypoparathyroidism: a single-centre experience

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Background
Pediatric hypoparathyroidism is an orphan disease. Conventional management combines native and active vitamin D, calcium supplementation and sometimes phosphate binders. The use of teriparatide has been reported both in adults (daily or bi-daily subcutaneous infusions) and in children (rather continuous subcutaneous infusion) as second-line therapy.
Methods
We present as median (min-max) the results of a retrospective single-centre review of medical charts of all children receiving teriparatide in our centre from 06/2016 to 12/2018.
Results
At a median age of 11.2 (3.7–15.5) years, Schwartz eGFR 109 (85–205) ml/min per 1.73 m^2, calcium 1.88 (1.62–2.17) mmol/l, phosphate 2.39 (1.74–2.79) mmol/l thus corresponding to SDS of 3.9 (1.1–5.6), 25-D 81 (47–112) nmol/l, teriparatide therapy was introduced in nine patients at the dose of 20 µg twice daily (1.04 (0.45–1.48) µg/kg/day), with further adjustment depending on calcium levels. Eight of them directly received intermittent supplementation when one patient briefly received continuous teriparatide infusion with a switch to intermittent supplementation after 4 months. The causes of hypoparathyroidism were CaSR mutation ($n=4$), APECED syndrome ($n=2$), post-surgical hypoparathyroidism due to Cowden syndrome ($n=1$), Di George syndrome ($n=1$) and hypoparathyroidism of unknown etiology ($n=1$). With a median follow-up of 1.4 (0.4–2.4) years, all patients still receive teriparatide. Severe side effects were reported in one child, namely two episodes of severe hypocalcemia and one of iatrogenic hypercalcemia. Other side effects were milder (lumbar pain, moderate hypocalcemia and dysgueusia). At the last follow-up, teriparatide dose was reduced in 6 children; median age was 11.8 (5.3–17.7) years, Schwartz eGFR 94 (79–162) ml/min/1.73m^2, calcium 1.98 (1.80–2.20) mmol/l, phosphate 1.9 (1.5–2.2) mmol/l thus corresponding to SDS of 2.1 (−1.1 to 3.16) ($P<0.01$), and 25-D 66 (35–119) nmol/l. Calciuria and calcium/creatinine ratio remained stable. On the renal ultrasounds, neither nephrolithiasis nor nephrocalcinosis appeared. Among children with pre-existing nephrocalcinosis, one worsened from stage 1 to 2, whilst the other two remained stable. Five children required the reintroduction of low doses of vitamin D analogs.
Conclusion
Intermittent teriparatide therapy decreases phosphatemia with a better control of calcemia and without any changes in calciuria. Thus, it appears to be a safe option in children refractory to conventional treatment. Long-term larger studies are required to confirm these data.
Disclosure
The authors declared no competing interests.
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P144

A multi-criteria decision analysis of the value of burosumab for the treatment of paediatric patients with X-linked hypophosphatemia in Portugal

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Objectives
Burosumab is an anti-FGF23 fully human monoclonal antibody, recently approved for the treatment of X-linked hypophosphatemia (XLH), presenting a novel treatment approach compared to conventional therapy (CT), composed of oral phosphate and active vitamin D. The objective of this study is to perform a Multi-Criteria Decision Analysis (MCDA) to assess the value of burosumab for the treatment of paediatric patients with XLH in Portugal, in comparison to CT.
Methods
MCDA is a method that provides a comprehensive and systematic assessment of therapies' value. A framework, developed specifically for the assessment of orphan drugs, consisting of 14 criteria related to the burden of disease (4), therapeutic value (7) and economic burden (3) was used. Eight national stakeholders, including four physicians, two patient representatives, one health economist and one health policy decision-maker, participated in a two-round process. In the first round, all participants established the relative weights (importance) of each criterion by the means of a preference elicitation adaptive questionnaire related to orphan drugs in general, while in the second round, both burosumab and CT were assessed by all physicians and one patient representative

against the pre-established criteria. Results from the first and second rounds were then combined to provide a global score for each treatment alternative out of 100.
Results
In the first round, criteria related to the therapeutic value were weighted higher than disease burden and economic impact related criteria. Treatment clinical impact, treatment safety and tolerability, and disease severity were the most valued criteria, with relative weights of 9.80%, 9.72% and 8.71% of the total score, respectively. On the other end, rarity of the disease, direct medical costs and direct non-medical costs were the least valued criteria, contributing with 3.79%, 4.55% and 4.59% of the total score, respectively. Second round results and global scores for both treatment alternatives will be presented in the poster.
Conclusion
This MCDA's first round results demonstrated that therapeutic value related criteria are the most valued criteria for the assessment of orphan drugs, based on different Portuguese stakeholders' preferences.
Disclosure
This study was funded by Kyowa-Kirin Portugal.
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P145

Nine-month follow-up data on biochemical, clinical, radiological and functional parameters in a clinical cohort of children at Evelina London Children's Hospital with X-linked hypophosphataemia treated with Burosumab

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Burosumab, a monoclonal antibody targeting fibroblast growth factor 23, is now available for clinical use in children with X-linked hypophosphatemia (XLH). We aimed to explore the effects of burosumab in children with XLH in a clinical setting, considering:

a) Biochemistry
b) Growth
c) Lower limb deformity (LLD)
d) Radiology
e) Motor function

Methods
Clinical/biochemical data were reviewed at 6 ($N=8$) and 9 ($N=9$) months for a cohort of children with XLH started on burosumab. Motor function was assessed with 6-minute walk test (6MWT). Radiographs were scored by a consultant radiologist. Paired t-tests were performed (significance = $P<0.05$).
Results
Mean age at commencement was 7.0 years (range = 1.6–16.7). Mean starting dose was 0.6 mg/kg, increasing to 1.1 mg/kg and 1.3 mmol/kg at 6 and 9 months.
Biochemistry
All patients initially had low/low-normal serum phosphate levels that improved and normalised with burosumab. Mean ± S.D. levels were 0.7 ± 0.1 at baseline, 1.0 ± 0.2 at 6 months, and 1.1 ± 0.1mmol/l at 9 months ($P<0.001$). ALP levels were initially raised (Mean ± S.D. 412 ± 69IU/l) with reduction into normal range by 9 months (Mean ± S.D. 310 ± 89 IU/l, $N=8$, $P<0.01$). All patients had low calculated renal tubular reabsorption of phosphate (TmP/GFR), which increased from Mean ± S.D. 0.57 ± 0.11 (RR = 1.15–2.44) to 1.07 ± 0.15 at 6 months ($N=9$, $P<0.001$) and 0.96 ± 0.12 at 9 months ($N=8$, $P<0.001$). PTH and urinary calcium:creatine ratios remained normal.
Growth parameters
Height Z-scores significantly increased, with Mean ± S.D. −2.60 ± 0.87 at baseline and −2.38 ± 0.87 at 9 months $P<0.01$.
Lower limb deformity
LLD was recorded in 7 children; varus ($N=4$), valgus ($N=2$), and windswept ($N=1$). The most severely affected patient, with initial intermalleolar distance of 10 cm, noted progression of deformity on treatment. All others noted an improvement at 9 months ($N=5$), with straightening evident in photographs and reduction of intercondylar or intermalleolar distances.
Radiology
Thatcher score (maximum score 10) improved in 6 patients at 6 months and was unchanged in three patients (Mean ± S.D. decreased from 2 ± 1.9 to 0.5 ± 0.4, $P=0.02$).
Motor function
6MWT ($N=4$) distances improved but were all still below normal reference range by at least 130 m. Mean ± S.D. was 258 ± 87m at baseline and 402 ± 82m at 6 months.
Conclusion
In a single UK centre, burosumab treatment of children with XLH improves biochemical markers, growth, LLD, radiological scores and 6MWT.
Disclosure
Moira S Cheung is on Advisory Board for Kyowa Kirin.
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P146

Does prior bisphosphonate therapy in children and adolescents with cerebral palsy alter surgical outcomes?

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Background
Children and adolescents with cerebral palsy (CP) experience musculoskeletal complications including spinal deformities, hip dysplasia and disuse osteoporosis. Bisphosphonates can improve bone mineral density, prevent fragility fractures. It is unclear if prior bisphosphonate use modifies post-operative complication in children with CP. Our aim was to compare surgical complications in children with CP with and without previous bisphosphonate treatment.
Methods
This retrospective observational cohort study reviewed all children presenting to Children's Hospital at Westmead bone and mineral clinic and orthopaedic clinic between 2000 and 2016. Cases were defined as children with CP who had received at least one dose of bisphosphonates (Zoledronic acid) prior to surgical correction of their hip or spine deformity. Controls were matched to cases based on age at surgery, GMFCS classification and sex (where possible) by investigators blinded to post-surgical complications. Complications were divided into four categories: Fractures, hardware malfunction, infection and others. The primary outcome was the percentage of any post-surgical complications. Secondary outcomes included the length of hospital stay and duration of immobilization. Unpaired T-Tests and Chi-Square tests were used to compare outcomes between groups.
Results
Twenty-two individuals with CP met inclusion criteria of which 11 cases underwent spinal surgery and 11 had hip surgery. These were compared to 25 bisphosphonate naive controls. The mean age at the time of surgery was 12.7 years (S.D. 3.3). Any cause post-operative complications were similar in both groups (cases 59% vs. controls 36%; $P=0.15$). When considering only children who had undergone spine surgery, any cause complications were significantly higher in the bisphosphonate group (cases 66.7% vs controls 26.7%; $P=0.02$). The majority of these post-operative complications (47%) were categorized as fractures or hardware malfunction. Secondary outcomes were similar between groups ($P > 0.05$).
Conclusion
To our knowledge, this is the first study comparing orthopaedic surgical outcomes between children who had previously received bisphosphonates and those who were bisphosphonate naive. Post orthopaedic surgery complications were similar between groups, however, cases had more complications after spinal surgery than controls. Prospective studies with larger cohorts are needed to clarify the impact of bisphosphonates on orthopaedic post-operative outcomes.
Disclosure
The authors declared no competing interests.
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P147

Changes in DXA Z-scores during bisphosphonate (BP) therapy in patients with osteogenesis imperfecta (OI) at a tertiary care hospital in South Africa

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Objectives
The aim of this study was to evaluate and assess the change in bone mineral density in OI children treated with BPs at Chris Hani Baragwanath Academic hospital (CHBAH), South Africa.

Methods
Medical files of 104 OI patients who were seen at Metabolic Bone clinic from 01 January 2006 till 31 December 2015 were reviewed. DXA measurements were available on 33 patients that received bisphosphonates from baseline and during therapy at three time points (9–18 months, 18–30 months and >30 months). Three methods using white male and female reference values for calculating bone mineral content (BMC) and bone mineral density (BMD) Z-scores on whole body less head (WBLH) and lumbar spine (LS) were applied and analysed as follows: 1) Calculated Z-scores using the Zemel Default (1,2) and 2) Height adjusted Z-scores for >5 year old children only (1) and 3) DXA machine calculated Z-scores.
Results
WBLH BMC and BMD Z-scores and LS BMC and BMD Z-scores showed significant increases over 30 months of treatment ($P<0.01$). The mean BMC and BMD Z-scores (WBLH and LS) at baseline were < −2 confirming low bone mass. Mean calculated Z-scores after 30 months had reached a Z-score > −2; mean height adjusted Z-scores reached a Z-score > −2 from 9–18 months onwards and mean DXA machine calculated Z-scores reached a mean Z-score > −2 after 18 months. At baseline, 83% of patients had a LS BMD height adjusted Z-score < −2 and after 30 months of BPs treatment, none of the patients had a LS BMD height adjusted Z-score < −2 ($P<0.001$).The mean fracture rate at baseline prior to BP therapy was 16.44 (95% CI: −1.98 to 34.85) and significantly decreased to 0.62 (0.27–0.97) at 9–18 months and to 1.1 (0.49–1.65) at >30 months ($P<0.001$) during BP therapy.
Conclusion
Bisphosphonate therapy significantly increased height adjusted LS BMD Z-scores to > −2 and decreased the number of fractures after 9–18 months of treatment in South African OI patients thus supporting the use of BPs in OI patients to minimise hospitalisation and treatment costs related to fractures.
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P148

Management of foramen magnum stenosis in patients with achondroplasia: relative merit of clinical and radiological indications for foramen magnum decompression

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Introduction
Achondroplasia, the commonest skeletal dysplasia, is caused by specific variant(s) in the fibroblast growth factor receptor 3 (FGFR3) gene that cause abnormal spine, skull and limb bone growth. Surgical indications for foramen magnum stenosis in this population vary widely in the literature.
Methods
We performed a retrospective analysis of patients with achondroplasia aged >20 years ($n=33$) in our regional skeletal dysplasia clinic. Where MRI scans were performed, the first scan was used for analysis of skull base landmarks and angles. Foramen magnum anatomy was categorised according to a recently proposed Achondroplasia Foramen Magnum Severity Score (AFMSS). Indications for MRI, surgical details, and clinical outcome data were collated from patients' files.
Results
MRI scans were performed in 63.6% (21/33) patients, mean age of first scan 4.8 years (range 3 months – 16 years). Clinical indications for MRI: upper motor neuron signs (24%), respiratory problems, e.g. apnoea (19%), increasing head circumference (19%); and alongside spine MRI for spinal deformities (19%), screening (19%). No patients who did not undergo MRI scanning had, nor developed, abnormal neurology. Scans showed FM narrowing on all and were classified AFMSS grade 1 (craniovertebral junction narrowing alone, $n=5$), grade 2 (loss of CSF space, $n=8$), grade 3 (cervical spinal cord flattening, $n=4$) and grade 4 (with cervical spinal cord signal change, $n=4$). Foramen magnum decompression (FMD) was undertaken due to clinical signs of myelopathy in 3 patients (9.1% of cohort); these patients' MRI all showed cervical cord signal change (AFMSS grade 4). Clinical outcomes post FMD neurosurgery: improved motor power ($n=1$), unchanged neurology ($n=2$). Patients with sleep apnoea ($n=3$) had AFMSS Grade 3 and no surgical intervention: one progressively improved and two showed no deterioration.
Conclusion
90% of our cohort had good outcome with no neurosurgical intervention. All those scanned had abnormal foramen magnum on MRI, all except those with clinically evident myelopathy were treated conservatively, including the 4 with cervical cord flattening without signal change. Intra-spinal cord signal change was the only radiological abnormality directly associated with FMD ($P=0.02$) which was accompanied by clinically evident myelopathy in all. Clinical abnormalities, rather than radiological scores, give reliable indications for neurosurgical intervention.
Disclosure
The authors declared no competing interests.
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P149

Bone mineral changes in 43 children with osteogenesis imperfecta treated by pamidronate

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Objectives
The purpose of our study was to evaluate the bone mineral accrual in children with osteogenesis imperfecta (OI) treated by pamidronate (PAM).
Methods
In retrospective study 43 children with different types of OI were included: 17 boys (39.5%) and 26 girls (60.5%). According to clinical OI, patients were: OI I type -13 (30.2%), OI III type – 24 (55.9%) OI IV type – 4 (9.3%), OI V type 1 (2.3%) and Bruck syndrome 1 (2.3%). The standard protocol with cyclic PAM infusions (3 consequent days 3–4 times in a year) was applied in annual cumulative dose ranged from 9 to 12 mg/kg. The observation period was 24 months. Bone mineralization parameters were detected by dual-energy X-ray absorptiometry of lumbar spine L1–L4 (densitometer Hologic QDR 4500C, with pediatric reference database). We evaluated bone mineral density (BMD) - Z-score, measured in standard deviations and deficiency in percentages. All patients were divided into 2 groups: 1st group (mild-OI I type) and 2nd group (moderate-severe, all other types).
Results
During 2 years of PAM treatment we have observed BMD-Zscore accrual ($P=0.000001$), decreasing the BMD deficiency ($P=0.0007$) and fracture rate reduction ($P=0.003$). BMD-Zscore increased from −3.2 (−4.5; −2.2) SD to SD in 1 year ($P=0.0003$); −2.4 (−3.7; −1.4) SD in 2 years ($P=0.005$). The deficiency of BMD changed from −34.0% (−22.0; −46.0) to −27.0% (−17.0; −38.0) in 1 year ($P=0.0001$); −23.0% (−12.0%; −26.0%) in 2 years ($P=0.00009$). Patients with OI I type had more intensive bone mineral accrual compare to moderate-severe patients: in 1 year: BMD Zscore +50.0% (4.9–68.4) vs +3.2% (0–15,9), $P=0.077$; BMD deficiency +13.0% (4.2–31.8) vs +5.6% (2.6–29.4), $P=0.022$; in 2 years: BMD Zscore +53.7% (24.6–67.1) vs +14.3 (5.6–20)%, $P=0.01$; BMD deficiency +34.3% (24–54.1) vs +16.4% (4.7–26.8), $P=0.022$; CONCLUSION: PAM treatment was effective in bone mineral accrual and fracture reduction. Patients with mild form of OI increased BMD more effective then moderate-severe forms.
Disclosure
The authors declared no competing interests.
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P150

Osteogenesis imperfecta: skeletal outcomes after bisphosphonates discontinuation at final height

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Objectives
Intravenous cyclical bisphosphonates are widely used to treat children with moderate to severe osteogenesis imperfecta (OI). They increase bone mineral

density (BMD), diminish fracture rates and improve mobility. Bisphosphonates are often discontinued when growth is completed. We aimed to determine if the skeletal gains achieved with bisphosphonates persist after their discontinuation in patients with OI.
Methods
We assessed patients with OI who had started intravenous bisphosphonates (either pamidronate or zoledronate) before 13 years of age, were treated for at least two years and discontinued treatment after completion of growth. Lumbar spine (LS) densitometry by dual-energy x-ray absorptiometry and radius peripheral quantitative tomography were performed at treatment discontinuation (baseline) as well as at two and four years thereafter. Spine radiographs were performed at baseline and four years.
Results
Thirty-one patients (22 females) had performed LS densitometry at baseline, two and four years. Patients had started treatment between ages 0.1–12.6 years and had stopped 4.7–15.7 years later, when their age ranged between 13.4–20.0 years (mean: 16.4 years (SD: 1.8)). Baseline LS areal (a) BMD was lower than in healthy individuals (mean z-score: -1.8 (SD: 1.2) and increased by 3.6% at two years and by 3.6% at four years ($P<0.05$). Baseline trabecular volumetric (v) BMD was inferior than in healthy individuals (mean z-score: -1.2 (SD: 3.3) and decreased by 9.9% at two years and 18.7% at four years ($P<0.05$), while baseline cortical vBMD was higher than in healthy individuals (mean z-score: $+0.8$, SD: 2.1) and increased by 2.9% at two years and 3.8% at four years ($P< 0.05$). No patient sustained a new vertebral compression fracture at four years of follow-up. The proportion of patients with new long-bone fractures in the two years before treatment discontinuation decreased compared to the last two years of follow-up (42% and 16%, respectively; $P<0.05$).
Conclusion
In patients with OI, stopping bisphosphonates after completion of growth was not associated with a decline in lumbar spine aBMD nor an increase in fractures at four years. Trabecular density at the radial metaphysis decreased, possibly from disappearance of bisphosphonates-induced metaphyseal transverse lines.
Disclosure
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Frank Rauch: PreciThera Inc (study grant).
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P151

The safety and efficacy of denosumab versus zoledronic acid in the treatment of pediatric osteoporosis: a randomized controlled pilot trial
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Objectives
Denosumab (Dmab) is a monoclonal antibody targeting RANKL administered by sub-cutaneous injection. Given its convenient mode of administration, our goal was to assess the safety and efficacy of Dmab compared to intravenous zoledronic acid (ZA) in pediatric osteoporosis.
Methods
In this one-year pilot study (NCT02632916), children 4–16 years with low-trauma fractures due to osteoporosis were randomized 1:1 to receive ZA 0.025 mg/kg or Dmab 1 mg/kg every 6 months (total of 3 doses), followed by calcium supplementation for at least 10 days following each dose. The primary outcome was the proportion of children with at least one episode of hypocalcemia at 48-hours post-dosing. 12-month changes in bone mineral density Z-scores (BMDZ), Spinal Deformity Index (SDI), and the incidence of long bone fractures were assessed with blinding to treatment. Adverse events (AEs) were reported. As a pilot study, all measures but the primary outcome were reported descriptively.
Results
Ten children were enrolled in and completed the study (4 with Duchenne muscular dystrophy and 1 with juvenile osteoporosis in each group, all boys). 80% on ZA had at least one episode of asymptomatic hypocalcemia vs none on Dmab ($P=0.01$). The mean $\pm$ standard deviation (SD) changes in BMDZ in the ZA versus Dmab groups were: lumbar spine (areal) $+1.1\pm0.7$ vs $+0.4\pm0.4$; hip (areal) $+0.7\pm0.5$ vs $+0.02\pm0.2$; tibia (volumetric) -0.2 ± 1.7 vs -0.05 ± 0.5). At baseline, the median SDI on ZA was 2 (range 0, 6) vs 0 (range 0, 1) on Dmab, and remained unchanged in both groups at 12 months. Two children sustained low-trauma non-VF (1 radius, 2 femur) on ZA compared to none on Dmab. AEs deemed related to the study drug occurred in 100% on ZA versus 40% on Dmab, none of which were serious. First exposure AEs occurred in 100% of patients on ZA compared to none on Dmab.
Conclusion
In this pilot study, hypocalcemic episodes and side effects were fewer on Dmab compared to ZA, and vertebral fractures stabilized in both groups. These data support further study of Dmab in children with osteoporosis.
Disclosure
Leanne Ward has been a consultant to and participated in clinical trials with Novartis Pharmaceuticals and Amgen Inc.
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P152

An evaluation of the rebound phenomenon during denosumab therapy in children with low turnover osteoporosis
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Objectives
Denosumab (Dmab) is a monoclonal antibody targeting RANKL administered by sub-cutaneous injection. Recent reports have raised concern about the 'rebound phenomenon' (hypercalcemia and increases in bone turnover markers, BTM) following Dmab in adults, and during treatment in children with osteogenesis imperfecta. The purpose of this report was to explore this phenomenon in children with osteoporosis associated with lower bone turnover.
Methods
In this one-year pilot study (NCT02632916), children 4 to 16 years with low-trauma fractures due to osteoporosis were randomized 1:1 to receive ZA 0.025 mg/kg or Dmab 1 mg/kg every 6 months (two doses). Serum ionized calcium and BTM were collected on the day before each dose (c-telopeptide of type I collagen (CTX), and bone-specific alkaline phosphatase (BSALP)). BTM were expressed as age- and gender-matched z-scores (Z).
Results
Ten children completed the study (four with glucocorticoid-treated Duchenne muscular dystrophy (DMD) and one with juvenile osteoporosis (JO) in each group, all boys). At baseline, the two boys with JO had a bone formation rate/bone surface by trans-iliac biopsies at Z -3.3 and -1.0. In DMD at baseline, the mean $\pm$ standard deviation serum CTXZ and BSALPZ were -2.6 ± 0.3 and -2.9 ± 0.6, respectively. There were no episodes of hypercalcemia preceding any treatment doses. CTXZ increased between baseline and six months, or between six and 12 months, in 5/5 boys on Dmab (greatest median change during either time period 22%; range 11, 165%) vs 4/5 on ZA (median change 11%; range 4, 14%). The BSALPZ increased in 3/5 boys on Dmab (median change 3%; range -17, 49%) vs 3/5 (median change 12%, range -6.0, 15). On Dmab, the CTXZ was below -2.0 in all but one patient with DMD (Z -1.7 for this patient) at 12 months, but was above-average (Z $+0.3$) for the patient with JO.
Discussion
In this pilot study, CTXZ increased above baseline more frequently on Dmab compared with ZA. BTM increases were greatest in the patient with JO on Dmab. In contrast, boys with DMD on Dmab had minimal BTM increases; furthermore, BTM remained low in DMD at 12 months.
Disclosure
Leanne Ward has been a consultant to and participated in clinical trials with Novartis Pharmaceuticals and Amgen Inc.
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P153

Long-term growth hormone treatment alters glucose metabolism in achondroplasia

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Objective
To investigate the effect of growth hormone (GH) treatment on glucose metabolism in achondroplasia (ACH) patients.
Patients and methods
Twenty-five GH-treated (0.35 mg/kg/week) ACH patients (10 males and 15 females) were included in this study. Oral glucose tolerance test (OGTT) was performed at three time points; 'pre-treatment' (age: 4.0±1.9 years), 'post short-term treatment' (age: 6.5±3.0 years), and 'post long-term treatment' (age: 11.8±3.4 years). We evaluated homeostasis model assessment of insulin resistance (HOMA-IR, fasting insulin (μU/mL) × fasting glucose (mg/dL) / 405) and β cell function by calculating insulinogenic index (IGI, Δinsulin (μU/mL) / Δglucose (mg/dL)). Statistical analysis was performed with Mann-Whitney's U test or analysis of variance (ANOVA) followed by multiple comparison using Tukey's test.
Results and discussion
No patients were diagnosed as diabetes mellitus throughout the observation period. Prediabetes was detected at least one time point in 32% (8/25) of the patients before or after initiation of GH administration (prediabetes group). GH treatment increased both HOMA-IR (pre: 0.7±0.4, post short-term: 1.9±1.2, post long-term: 2.2±0.9, $P<0.01$) and IGI (pre: 0.25±0.19, post short-term: 0.98±0.42, post long-term: 1.02±0.51, $P<0.05$), although the increase was within normal range. There was no difference in HOMA-IR between the prediabetes and the normal groups at pre-treatment or post long-term GH treatment. However, in the prediabetes group, HOMA-IR was higher at post short-term GH treatment (2.6±1.5 vs 1.6±0.8, $P<0.05$). IGI was lower at pre-treatment in the prediabetes group than in the normal group (0.06±008 vs 0.38±0.05, $P<0.01$), but there was no significant difference during GH treatment.
Discussion and conclusion
Although residual β cell function sufficiently counteracts insulin resistance induced by GH, OGTT may demonstrate prediabetes in ACH patients with low β cell function. Since low IGI at pre-treatment and/or marked increase of HOMA-IR at post short-term GH treatment seems to be related to transient prediabetes, vigilant monitoring of glucose metabolism should be performed when administrating GH to ACH patients with these findings.
Disclosure
The authors declared no competing interests.

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P154

Self-reported sedentary time is negatively associated with microarchitecture of the tibia

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Objectives
Weight bearing physical activity (PA) is thought to be beneficial to bone mineral accrual in childhood, but the influence of PA and sedentary time on bone microarchitecture is less well described. We examined the relationships between self-reported PA and volumetric bone mineral density (vBMD) and bone microarchitecture at the distal tibia, assessed using high resolution peripheral quantitative computed tomography (HR-pQCT).
Methods
Healthy children aged 7–17 years were invited to participate. Participants were asked how many hours per day they spend asleep or doing activities whilst lying or seated ('sedentary time') and doing exercise during which their heart rate increases or they sweat ('strenuous PA'). Habitual PA was also assessed using the Physical Activity Questionnaire (PAQ). vBMD and bone microarchitecture of the tibia were measured by HR-pQCT (XtremeCT, Scanco Medical AG, Switzerland). Associations between measures of PA and bone outcomes were assessed using linear regression adjusting for age, sex and height.
Results
88 children participated; mean age 12.5 years (SD 2.4), 61% male. Reported sedentary time (median 19.0 hours/day, IQR 17.0–21.5) correlated negatively with strenuous PA (median 1.0 hours/day, IQR 0.5–1.5), $r=-0.36$, $P=0.001$. Sedentary time was negatively associated with total vBMD, cortical area, cortical vBMD, cortical thickness and trabecular thickness, but not trabecular number or separation. In contrast, strenuous PA was positively associated with total vBMD, cortical area, cortical thickness, and trabecular thickness, with similar positive relationships between habitual PA (PAQ score) and total vBMD, cortical area and thickness. When both sedentary time and strenuous PA were include in the regression model, sedentary time was significantly negatively associated with cortical area ($\beta=-7.3$ mm^2 per 2 hours/day, $P=0.003$), cortical thickness ($\beta=-0.07$ mm per 2 hours/day, $P=0.01$), cortical vBMD ($\beta=9.91$ g/cm^3 per 2 hours/day, $P=0.02$) and trabecular thickness ($\beta=-0.002$ mm per 2 hours/day, $P=0.05$), whereas the associations with strenuous PA were no longer statistically significant.
Conclusion
High levels of sedentary time might be detrimental to tibia microarchitecture, whereas strenuous physical activity, after adjustment for sedentary time, is not associated with tibia vBMD or microarchitecture.
Disclosure
The authors declared no competing interests.

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P155

Gender specific paediatric reference data for muscle function parameters assessed using jumping mechanography

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Objective
Bone adapts to mechanical stimuli by increasing its mass and changing geometry; muscles are the stimulators for this change as they induce forces through contractions. Thus, bone strength is driven by muscle function. Research has shown that muscle mass and muscle function may not be proportional and hence analysing muscle function becomes of crucial importance. Here we propose to establish gender specific paediatric reference data for muscle function parameters assessed using jumping mechanography in Indian children.
Methods
The data presented here includes 562 apparently healthy Indian children (293 boys, 269 girls) aged 6 to 15 years. Children were recruited from 3 urban schools having similar (Middle to Upper) socio economic status. Participants performed 2 tests, single two legged jump and multiple one legged hopping, on a portable ground reaction force platform (Leonardo Mechanograph, Novotec).The single two legged jump is a counter movement jump with freely moving arms. The main outcome parameters of this test are maximum power (Pmax) and Pmax/mass. In multiple one legged hopping, the children were instructed to repeatedly hop on one leg. The maximum voluntary force (Fmax) and its relation to body weight Fmax/Body Weight is evaluated through this test. LMS method was used to generate age specific reference smooth curves.
Results
Pmax and Fmax were seen to be strongly dependent on age, in both the genders. Both parameters steadily increased in boys and reached a plateau in girls at around 13 years. Our children, however, showed lower maximum power and maximum voluntary force when compared with machine reference data as well as lower maximum relative power (Pmax/mass) and maximum relative force (Fmax/BW) when compared to other available reference data1. The Esslinger Fitness Index (EFI – maximum relative power normalized to age and gender) and Fmax/BW decreased with increase in age.
Conclusion
Muscle function parameters of healthy Indian children appear to be different from their western counterparts; these differences may be attributed to differences in dietary habits and physical activity. We present here reference values for muscle function by jumping mechanography in Indian children, these may be useful for the assessment of muscle function.
Disclosure
The authors declared no competing interests.

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P156

Patients with nephropatic cystinosis display lower cortical thickness and grip strength

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Objective
Nephropathic cystinosis is an orphan autosomal recessive lysosomal storage disease characterized by a deficiency of cystinosin, a cysteine transporter protein, encoded by CTNS. As a consequence of the disease cystine crystals accumulate leading to tissue damage, primarily in kidney and cornea. With improved medical care, new challenges like skeletal complications are a matter of concern. Only few data are available dealing with bone development. The aim of our study is to gain more information on bone density and geometry in these patients.
Methods
In forty-one patients (24 males, 17 females) with genetically proven nephropathic cystinosis a standard evaluation was performed including history, physical examination, biochemistry, grip strength and imaging studies. Bone mineral density (BMD), bone geometry and muscle cross sectional area were measured using peripheral quantitative computed tomography (pQCT, XCT 2000). We compared results with age-and gender-specific reference data.
Results
Mean age at pQCT evaluation was 22.5 ± 9.79 (range 6.6–39.6). Patients mean z-scores for height −1.98 ± 1.50, weight −1.85 ± 1.20, ulnar length −1.99 ± 1.39 and BMI −1.10 ± 1.28 were significantly reduced ($P < 0.01$). In all, mean z-scores for trabecular −0.10 ± 1.65 and cortical BMD −0.38 ± 1.69 were within normal ranges. However, medullary cross sectional area was normal (−0.18 ± 1.23), together with a reduced total CSA (−1.38 ± 1.22), cortical CSA (−2.33 ± 1.05) was markedly reduced ($P < 0.01$). After adjustment for height, this mismatch was even more pronounced. Muscle CSA and strength strain index (SSI) were normal for patient's height, however, grip strength z-score reduced with −1.81 ± 1.13 (also after considering ulnar length). Grip strength z-scores correlated with cortical CSA z-scores ($r = 0.48$) and SSI-z-scores ($r = 0.45$) ($P < 0.01$).
Conclusion
In this study population, bone density parameters were within the normal range, but bone geometry was altered, leading to a thinner cortex with impact on bone stability. Muscle weakness as expressed by lower grip strength might be causative and therefore a matter of possible treatment opportunities with a long-term effect on quality of life.
Disclosure
The authors declared no competing interests.

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P157

Gonadotrophin releasing hormone analogues utilised in late and post-pubertal adolescents causes a reduction in bone density in transgender teenagers attending a national gender dysphoria clinic

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Objectives
Gender Dysphoria (GD) occurs when a person's gender identity differs from their biological sex. GID presenting in childhood can dissipate at puberty. If it persists, physical interventions commence with the use of a GnRH analogues (GnRHa) for one year followed by cross sex hormones.
Methods
Adolescents with a diagnosis of GD were reviewed in a national GD clinic at Leeds Teaching Hospitals, UK. Standardised medical assessments included clinical assessment of pubertal stage, hormone profile, bone biochemistry and bone density.
Results
Seventy seven adolescents who had been on GnRH analogues for a mean age of 1.2 years were reviewed. 41 were assigned female at birth (AFAB) and 36 assigned male at birth (AMAB). There was a reduction spine and total body density in both groups. In AFAB the spine density reduced from −0.10 SDS to −0.74 SDS, in AMAB it reduced from −0.67 SDS to −1.35 SDS. There was also a significant reduction in total body density values in AMAB, whereas AFAB had a downward trend. The BMI was unchanged in both sexes, but there was an increase in fat mass and reduction in muscle mass.
Conclusions
Short term use of GnRHa in late puberty caused a reduction in spine and total body density, increase in fat mass and reduction in muscle mass in adolescents and teenagers presenting to a national gender identity service.
Disclosure
The authors declared no competing interests.

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P158

Association of grip strength and body composition in Indian boys and girls

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Objectives
Association of grip strength (GS) with anthropometric parameters has been reported. Our objective was to assess grip strength in 6 to 18-year-old healthy Indian children (urban and rural) and study the association of GS with body composition.
Methods
This was a part of a multicenter, cross-sectional, observational school-based study; multi-stage stratified random sampling was carried out and children ($n = 1980$) from various urban ($n = 1041$, Girls: 556) and rural ($n = 940$, Girls: 474) parts of India were assessed (2016–2017). Anthropometric measurements, body composition by Bioelectric Impedance Analysis viz Fat-free Mass (FFM), Fat % (FATP), Fat Mass (FATM), Muscle Mass (MM) and grip strength measurements (digital hand dynamometer) were carried out.
Results
Mean age was 13.3 ± 2.2 years. Mean GS was significantly higher in boys (19.6 ± 9.17 kg) than in girls (14.3 ± 5.3 kg) ($P < 0.05$) and increased with age in both genders. After 12 years, an increase in GS plateaued in girls but not boys. Mean GS was significantly higher in urban (21.05 ± 9.7) than in rural boys (17.8 ± 8.2) ($P < 0.05$). Mean GS in urban (14.9 ± 5.2) and rural girls (13.8 ± 5.5) was comparable but significantly less than both urban and rural boys ($P < 0.05$). Positive significant correlations of GS were observed with FATM, FATP, FFM, and MM. Degree of correlation varied, with highest being in urban boys (0.82 for FFM and MM, 0.35, 0.17 for FFM and FATP) and then gradually decreasing in the order of rural boys (0.73 for FFM and MM, 0.25, 0.15 for FFM and FATP), urban girls (0.53 for FFM and MM 0.39, 0.33 for FFM and FATP) and rural girls (0.42 for FFM and MM 0.30, 0.31 for FFM and FATP) ($P < 0.05$ for all). To normalize for FFM, GS for FFM ratio was computed. In boys, GS for FFM ratio increased with age, in girls, after 14 years of age, a decrease was noted.
Conclusion
Age-dependent increase in GS was strongly related to FFM. Lower GS in rural children and in girls is a matter of concern and needs urgent attention.
Disclosure
The authors declared no competing interests.

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P159

Determinants of muscle function in 6 to 11 year old rural Indian children

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Objective
Children in rural areas have inadequate nutritional intake, hence their muscle function may be compromised. The objective of this study was to study the determinants of muscle function in rural Indian school going children.
Methods
We cross sectionally studied 232 prepubertal school going children (106 girls) aged 6–11 years, from 2 different villages in rural area around Pune city in July 2018. Height, weight, body composition (bioelectrical impedance, TANITA) and muscle function (Jumping mechanography, Leonardo, Novotec) were measured. Physical activity and diet were recorded.

Results
Mean age was 8.9±1 years. Mean z scores for height, weight and BMI were −0.9±0.8, −1.2±0.8 and −1.1±0.9 respectively. Mean maximum power (Pmax) and mean maximum voluntary force (Fmax) (jumping mechanography) were 0.7±0.2 kW and 0.7±0.1 kN respectively. Both, Pmax and Fmax were positively correlated with fat percentage ($r=0.256$, $r=0.505$ respectively), fat mass ($r=0.336$, $r=0.571$ respectively), fat free mass ($r=0.834$, $r=0.819$ resp), muscle mass ($r=0.834$, $r=0.817$ respectively) ($P<0.05$ for all). To study the determinants, the muscle function, body composition, Protein intake and physical activity were classified with respect to their medians and used in regression. Regression analysis showed that FFM was a significant predictor for Pmax (Odds Ratio OR=20.01(7.6–52.4), $P<0.05$) while light physical activity showed marginal association (OR=2.28, (0.92–5.7), $P<0.1$), together explaining 50% of variability in Pmax. FFM and vigorous physical activity were predictors for Fmax (OR=11.44, (4.3–30.7); OR=2.53, (1.2–6.3) resp, $P<0.05$) and animal protein intake was also marginally associated (OR=2.3, (0.93–5.7), $P<0.1$). These variables predicted 50% of the variability in Fmax. Fat percentage above median was a negative predictor for both Pmax and Fmax (OR=3.57, (1.4–8.8); OR=14.45, (4.9–43.0) resp, $P<0.05$).
Conclusion
FFM, physical activity and animal protein intake were the determinants of muscle function in rural children, hence require special attention.
Disclosure
The authors declared no competing interests.
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P160

Assessment of muscle mass and function in Indian children with type 1 diabetes

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Objective
Type 1 diabetes (T1D) in one of the commonest chronic childhood disorders; poor muscle function and sarcopenia has been reported among T1D in adults. Reports on the impairment of muscle function are scarce in children. Our objective was to assess muscle mass and function in children with diabetes and study association of muscle mass and function with control of blood glucose (as measured by HbA1C) and disease duration.
Methodology
This was a cross sectional observational study conducted at a tertiary level pediatric endocrine and growth unit in Pune, India. Children with T1D with disease duration of >1 year with no other co-morbidity or associated illness were included in the study. Demographic data, anthropometric measurements, details of insulin treatment, disease duration and HbA1c were collected. Muscle mass was measured using iDXA (Lunar iDXA, GE Healthcare, WI, fan beam scanner, encore software – version 16) and sarcopenia index was calculated using the formula -Appendicular lean mass/body mass index (BMI). Muscle function was tested with 2 tests: a single two legged jump and multiple one legged hopping on a portable ground reaction force platform (Leonardo Mechanograph, Novotec).
Results
Data on 38 children were analyzed (20 boys and 18 girls), their mean age was 13.6±2.6 years and mean disease duration was 4.9±2 years. Their mean height, weight and BMI Z scores were −0.6±0.9, −0.6±0.9 and −0.4±0.9 respectively. Mean HbA1c in boys was 9.9% and in girls 9.8% ($P>0.05$). The mean Z scores in comparison with healthy Indian children, for maximum voluntary force, maximum voluntary force relative to body weight, maximum power and relative maximum power were −0.36±1, −0.2±1.1, −0.35±1.3 and −0.5±1.1 respectively. Mean sarcopenia index in girls was 684.9±233.7 and 662.2±170.3 m^2. On co-relation analysis, HbA1c had a significant negative correlation with sarcopenia index in boys ($R^2=-0.53$, $P=0.02$) but not in girls ($R^2=0.3$, $P=0.16$). Disease duration also had a negative correlation with power max in boys ($R^2=-0.5$, $P=0.01$) but not in girls ($R^2=0.24$, $P=0.3$).
Conclusion
Mean muscle function parameters were lower in children with diabetes in comparison with healthy controls. Poor glucose control and increasing duration of diabetes may increase the risk of compromised muscle function, especially in boys.
Disclosure
The authors declared no competing interests.
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P161

Endocrinological complications in Czech paediatric patients with Duchenne muscular dystrophy

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Objectives
Duchenne muscular dystrophy (DMD) is a rare hereditary X-linked muscular dystrophy affecting approximately 1:5.000 live borne males. The mobility and respiratory complications have been improved by implementing the glucocorticoid treatment in DMD, however, secondary osteoporosis, short stature and delayed puberty emerged as unwanted side-effects of the treatment. We aimed to evaluate the endocrinological complications in boys with DMD followed at our neuromuscular centre.
Methods
Boys with DMD followed at our neuromuscular centre were systematicaly screened for endocrinological complications. The screening protocol included physical examination, height and BMI measurement, blood tests, lateral X-ray of the spine and bone density assessment. We present the results of a pilot baseline evaluation of the patients.
Results
We were able to analyse the data in 34 boys with DMD, mean age was 10.2±3.5 years. Thirty boys (88%) were on corticosteroids (16 on prednison and 14 on deflazacort), and 24 boys (71%) were still ambulatory. Seventeen boys (50%) had body height below the 3. percentile, 13 (38%) had at least one vertebral compression fracture, 6 (18%) had positive history of a long bone fracture and 9 (26%) had lumbar spine bone mineral density (BMD) Z-score ≤ -2.0. In 3 boys out of 6 aged 15 years or more, gonadoliberin analogues were indicated due to delayed puberty. Based on these findings, bisfosfonate treatment was administered to 12 boys (35%).
Conclusions
According to our preliminary data, the endocrinological complications are common in boys with DMD. Our screening protocol proved to be useful in identifying patients at risk and implementing appropriate treatment approach. We intend to follow the cohort prospectively to describe further development of height, BMI and puberty and to monitor the effect of bisfosfonate treatment on BMD and fracture rate.
Disclosure
The authors declared no competing interests.
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P162

Bone monitoring and morbidity in adults with duchenne muscular dystrophy: Challenges in implementation of standards of care

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Background
Osteoporosis is common in subjects with Duchenne muscular dystrophy (DMD). Studies in paediatric DMD identified a high frequency of fragility fractures but there are no studies in the adult population. Recent updated international standards of care (2018) for children and adults with DMD recommend the following for bone monitoring:
- Lateral thoracolumbar spine x-rays to screen for vertebral fracture (1–2 yearly if on glucocorticoid; 2–3 yearly otherwise)
- DXA spine bone mineral density (BMD) annually

Objectives
This retrospective study aims to audit bone health monitoring according to standards of care and to report on radiologically confirmed fractures in adults with DMD.
Methods
Men with DMD aged ≥ 18 years in the adult neuromuscular or respiratory clinics (2013–2018) were included (n,41). Fractures and bone monitoring from 2013 till

September 2018 or time of death were evaluated. Results were expressed as median (range).
Results
Median age of the group was 24 years (19, 41). Eight (20%) died by last assessment, median age of death 23 years (20, 29). All were non-ambulant. 12/41(29%) had gastrostomy for feeding, 29/41 (71%) required assisted ventilation. 11/41 (27%) had metal instrumentation for scoliosis.10/41 (24%) were on glucocorticoid whereas 31/41 (76%) were glucocorticoid naïve or had received glucocorticoid < 12 months and had discontinued for longer than five years. 4/41 (10%) sustained new fragility fractures during the study period. 3/10 (30%) of those on glucocorticoid sustained fractures during the study period including a man with progression of pre-existing vertebral fractures presenting with severe back pain. On the other hand, 1/31 (3%) not on glucocorticoid sustained fractures during the study period. None had monitoring of vitamin D levels or screening lateral thoracolumbar spine x-ray. 12/41 (29%) had at least one DXA performed during the period. DXA BMD done in the adult service were not size adjusted. 6/41 (15%) had bisphosphonate therapy.
Conclusion
Fragility fracture may be underestimated in adult men with DMD as routine screening for vertebral fracture was not in place. There is a need to implement bone health monitoring in the adult population accordance with the updated standards of care.
Disclosure
The authors declared no competing interests.
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P163

Prenatal oligohydramnios is associated with hip shape in adolescent males

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Hip development is influenced by mechanical loading during fetal movement by joint and reaction forces equivalent to several times bodyweight. These forces increase with fetal size and gestation length, and are lower in oligohydramnios and breech presentation which are both risk factors for developmental hip disorders. However, associations between indicators of prenatal mechanical loading and hip shape in later life remain unexplored. We therefore examined associations between prenatal loading indicators (birthweight, gestation length, oligohydramnios, polyhydramnios and presentation at birth) and hip shape in late adolescence in 2004 participants (1086 female) from the Avon Longitudinal Study of Parents and Children (ALSPAC). Prenatal indicators were obtained from obstetric records, and hip shape was quantified using dual-energy X-ray absorptiometry (DXA) images taken at age 17 years from which hip shape modes (HSMs) were generated. Associations were examined in models adjusted for sex, and potential confounders (maternal education, maternal smoking, parity, maternal age). 21 participants had oligohydramnios, 19 had polyhydramnios and 103 had breech presentation. Birthweight was positively associated with HSM1, and negatively associated with HSM2 and HSM5, whilst gestation length was positively associated with HSM4 and HSM5. There was little evidence of associations between polyhydramnios or breech presentation and hip shape. In contrast, oligohydramnios was associated with substantially lower HSM1 scores in males (-1.14 s.d., 95%CI -1.82s.d. to -0.45s.d.) but not females (0.08s.d., -0.47 to 0.63 s.d., sex interaction $P=0.006$). Oligohydramnios was also associated with lower HSM7 scores in both sexes (-0.43s.d., -0.86 to -0.01s.d., sex interaction $P=0.788$), and with greater HSM8 scores in males (1.05s.d., 0.38 to 1.71s.d.) but not females (0.23s.d., -0.33 to 0.78s.d., sex interaction $P=0.063$). In males with prenatal oligohydramnios, the shape described by these HSM differences was characterised by narrower upper femur width, and differences in greater and lesser trochanter size and shape. Further adjustment for potential mediators (delivery method, and height, fat mass and lean mass at 17 years) did not affect results. These results suggest that prenatal skeletal loading may influence joint shape in adolescent males. In particular, oligohydramnios is associated with large differences in hip shape, although small sample size means replication is required.

Disclosure
The authors declared no competing interests.
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P164

Musculoskeletal deficits persist up to two years despite anti-TNF-alpha antibody therapy in children with Crohn's disease: Results of a prospective, observational inception cohort study

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Objectives
To evaluate musculoskeletal trajectories in children with newly diagnosed Crohn's disease (CD), and to determine whether children treated with anti-tumour necrosis factor-alpha antibody (anti-TNF, TREATED vs NAÏVE) had persistent deficits at two years.
Methods
This was a single-centre prospective, observational inception cohort study. Children with CD underwent assessments within 6.5 ± 9.5 days from diagnosis and annually for two years including: peak jump power (PJP) by jumping mechanography, serum bone turnover markers (BTM), tibia peripheral quantitative computed tomography, and lateral spine x-rays for vertebral fractures (VF).
Results
73 children were enrolled; 55 completed two years' follow-up. Thirty-five children were TREATED, 38 NAÏVE, mean age 14.3 ± 2.9 years, 65% boys. Anti-TNF was initiated on average at 9.6 ± 8.9 months. At baseline, age, bone age, anthropometry and the Pediatric Crohn's Disease Index (PCDAI) were similar, while serum alkaline phosphatase was lower in TREATED children (z-score (Z) median -1.5, range -2.9–2.3, vs -1.1, range -2.9–2.3, $P=0.035$). PCDAI decreased in both groups, but was higher in TREATED children at three, 12 and 24 months (all, $P<0.001$). Serum BTM, PJP, muscle cross-sectional area (CSA), and tibia bone measures improved in both groups (all compared to baseline, $P<0.028$), with the exception of cortical volumetric bone mineral density (vBMD), which declined (both groups, $P<0.001$). The largest improvements were in PJP (TREATED mean Z change $\pm$ SD $+1.8\pm1.4$ vs NAÏVE $+1.6\pm1.3$, both, $P<0.001$) and muscle CSA (TREATED $Z+0.9\pm0.8$ vs NAÏVE $+0.9\pm0.8$, both $P<0.001$), followed by trabecular vBMD (both, $P<0.015$) and cortical CSA (both, $P<0.024$). Despite normalization of BTM in both groups, only TREATED patients had residual deficits at two years (all, $P<0.017$ vs the healthy average). Cumulative glucocorticoid (GC) dose (mg/m^2) was higher in the TREATED vs NAÏVE patients ($P=0.016$). Two patients (1 NAÏVE, 1 TREATED) had two-year incident VF (one VF each, both mild).
Conclusions
Muscle strength, tibia muscle-bone structure and BMD improved significantly in children with CD undergoing specialist care regardless of treatment modality. Despite these improvements, at two years anti-TNF TREATED patients had higher PCDAI, higher cumulative GC exposure, and significant residual musculoskeletal deficits.
Disclosure
The authors declared no competing interests.
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P165

Fibroblast growth factor-21 (FGF-21) – marker of mineral bone disorder

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Introduction
FGF-21 is a protein that is produced by the liver and adipocytes. In patients with anorexia nervosa (AN), it could be involved in a complex adaptive response to starvation. In addition, this newly discovered protein could play pathogenic role in trabecular skeletal homeostasis. The aim of our work was to evaluate the concentrations of FGF-21 and bone metabolism in patients with AN.
Methods
Thirty seven female patients (aged 14.76 ± 3.99 years) with restrictive type of AN and 19 sex-matched healthy controls (aged 13.84 ± 8.17 years) were enrolled in this study. Laboratory parameters of bone metabolism including Ca, P, ALP, vitamin D, PTH, osteocalcin, CTx and PINP-l were examined. Bone mineral density (BMD) was assessed by dual x-ray absorptiometry (DXA).
Results
Patients with AN had significantly lower body weight in comparison to controls (40.4 ± 1.5 vs 49.3 ± 3.2 kg, $P \leq 0.05$). We observed no significant differences in plasma FGF- 21 between patients with AN and controls (113.50 ± 19.68 vs 128.62 ± 21.1 pg/ml, $P \geq 0.05$). There was no significant correlation between concentration of FGF-21 and parameters of bone metabolism. In patients with AN, significant correlations were found between body weight and BMD in the proximal femoral area ($r = 0.54$), as well as whole-body BMD ($r = 0.59$) and trabecular bone score (TBS) ($r = 0.5$), respectively. We found trend of correlation between TBS a FGF-21 ($r = -0.43$).
Conclusion
The trend of correlation between circulating FGF-21 and damaged trabecular microarchitecture in patients with AN could bring new insight into pathogenesis of 'osteopathic condition'. It seems that association between bone changes and mental anorexia creates a unique skeletal entity.
Disclosure
The authors declared no competing interests.

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P166

The ketogenic diet and bone density: a retrospective longitudinal cohort study

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Background
The Ketogenic Diet Treatment (KDT) is a well-established intervention for intractable childhood epilepsy and the first choice treatment for Gluccose-1-transporter-deficiency-syndrome and Pyruvate-dehydrogenase-complex deficiency. During long-term follow up of children treated with KDT an increased incidence of bone fractures has been found. However, the exact contribution of KDT to a decreased BMD remains unclear. Prophylactic supplementation with calcium and vitamin D is mandatory, but may fail to prevent continued bone mineral density (BMD) loss. Moreover, there is an increased risk of kidney stones. Treatment with bisphosphonates for a decreasing bone mineral density with or without fractures is not yet a regular part of treatment in these children.
Objective
This study aimed to evaluate changes in BMD measured with dual-energy X-ray Absorptiometry (DXA) in children treated with KDT and to evaluate whether treatment with bisphosphonates may be useful.
Methods
In this retrospective cohort study, all children who were treated with KDT from January 1st 2010 until August 1st 2018 at the Radboudumc Amalia Children's hospital were included. Patients had to have at least two DXA-scans to be eligible for inclusion. *Z*-scores of DXA-scans were compared over the course of time.
Results
Out of the 68 children who were treated with KDT, 20 patients were included (average time on KDT 39.55 months; range 9–100 months). The *Z*-score at the time of the first DXA-scan was −1.89. patients. A statistically not signoficant decrease in BMD was found. Four patients experienced fractures during KDT. Five patients received bisphosphonate therapy. We found an increased BMD in patients treated with bisphosphonate therapy. This was statistically significant in comparison to the non-bisphosphonate group ($P = 0.034$).
Conclusion
The ketogenic diet itself might be associated with decreased bone mass, and bone health monitoring is important in this high-risk group. Larger studies are required to further explore the relationships between the KDT and BMD, and longer-term follow up is required to determine fracture risk throughout life. Further therapy with bisphosphonate needs to be explored, as our results suggest that this might have a positive effect on bone mineral density
Disclosure
The authors declared no competing interests.

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P167

Children's multivitamins do not contain sufficient vitamin D

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Objective
Public Health England recommends that children in the United Kingdom (UK) aged over 1 year should take a vitamin D supplement containing 400 IU/day. Commercially available children's multivitamin and vitamin D supplements were surveyed to determine the vitamin D content.
Methods
Multivitamins and vitamin D supplements marketed at children <12 years and sold by nine UK supermarkets and health supplement retailers were surveyed. The vitamin D content was determined from manufacturer's websites and product packaging.
Results
67 multivitamins were surveyed, containing 0–800 IU/day vitamin D. Only 25–36%, depending on the child's age, provided ≥400 IU/day vitamin D. A further 24 products were available that contained only vitamin D or were marketed as for 'healthy bones'. The vitamin D content of these products was typically higher than for multivitamins (57–67% contained ≥400 IU/day), although ranged from 50–1000 IU/day.
Conclusions
Few multivitamin products that are available in UK supermarkets and high street health food shops supply the recommended 400 IU/day vitamin D. Clinicians need to be aware of this when recommending vitamin D supplementation and advise parents/carers to choose a product that contains ≥400 IU/day vitamin D.
Disclosure
The authors declared no competing interests.

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P168

Abstract withdrawn.

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P169

Rescue diet restores bone matrix mineralization in mice with a non-functioning vitamin D receptor

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Objectives
Mice with a non-functioning vitamin D receptor (VDR mutants) develop severe secondary hyperparathyroidism, which can be rescued by a diet enriched with calcium, phosphate and lactose. In this work, we studied the effects of a low calcium challenge (CD), normal calcium (ND) and a calcium enriched rescue diet (RD) on the bone mineralization density distribution (BMDD) and osteocyte lacunae sections (OLS) in these mice.
Methods
BMDD and OLS were measured in femoral bone from male VDR mutants ($n=22$) and wildtype (WT, $n=11$) mice based on quantitative backscattered electron imaging. Mice were fed with RD for 4 months (baseline), subsequently switched to CD for 2 months and afterwards fed 3 months either with CD, ND or RD (9 months age-groups).
Results
At baseline no difference in BMDD or OLS parameters between VDR mutants and WT could be observed. After 2 months with CD distinct differences in BMDD were observed, for instance average degree of mineralization CaMean was decreased by -7.6% and the percentage of low mineralized bone area CaLow was 3-fold ($P\leq0.001$) in metaphyseal spongiosa in VDR mutants versus WT, while OLS-parameters were similar. Comparison among the VDR mutant mouse groups revealed no differences in OLS but differences in BMDD. Of the 9 months old mice, only those on RD had similar BMDD compared to baseline.
Conclusion
Switching the VDR mutant mice from RD to CD for 2 months caused severe effects on BMDD showing a large percentage of bone area with poor mineralization consistent with histologic signs of rickets. These detrimental effects on bone mineralization could be rescued by following 3 months with RD which is in line with the previously reported correction of hyperparathyroidism. Our findings further suggest no change in osteocyte lacunae size, shape and density independent of differences in bone mineralization in VDR mutants.
Disclosure
The authors declared no competing interests.

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P170

Serum 25-hydroxyvitamin D requirements to prevent rickets in Nigerian children on a calcium-deprived diet

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Objectives
Nutritional rickets results from the interaction of poor vitamin D status and limited calcium intake. Vitamin D requirements are greater in children with limited intake of calcium. We sought to determine the serum 25-hydroxyvitamin D [25(OH)D] concentration that can prevent rickets in calcium-deprived Nigerian children.
Methods
We reanalyzed data from a case-control study of Nigerian children with active rickets (cases) and age-, sex-, and weight-matched control subjects without rickets in an area where dietary calcium insufficiency is common (J Pediatr 2000;137:367-73). Active clinical rickets was confirmed radiographically, and serum 25(OH)D was measured by immunoassay. We performed a multivariate logistic regression to assess the odds of rickets associated with varying 25(OH)D values, while adjusting for calcium intake and other risk factors.
Results
A total of 118 children with rickets and 117 control children had sufficient data ($n=235$) for multivariate analysis. Rachitic children had a mean ($\pm$SD) age of 51.3 ± 24.3 months, and 53 (45%) were male. Cases and controls had similarly low mean dietary calcium intakes (216 ± 89 and 209 ± 92 mg/day, respectively). In a model adjusted for weight for height and calcium intake, the odds ratio (95% confidence interval) for rickets was 13.8 (4.1–47) for 25(OH)D <30 nmol/L, 4.3 (1.6–11.6) for 30–39 nmol/L, 0.8 (0.3–2.5) for 40–44 nmol/L, and 0.13 (0.04–0.43) for ≥50 nmol/L, compared with the range of 45–49 nmol/L. In an unadjusted model, the area under the receiver operating characteristic (ROC) curve was 0.84, indicating a strong relationship of 25(OH)D with having rickets. In the fully adjusted model, the area under the ROC curve was 0.89.
Conclusion
In Nigerian children with a low dietary calcium intake of approximately 200 mg/day, a 25(OH)D concentration below 40 nmol/L was associated with nutritional rickets. These results emphasize the utility of the multivariable modeling approach in the study of 25(OH)D and calcium requirements to prevent rickets. In future studies, standardized 25(OH)D measurements, dietary calcium intake, life-style data, and a consistently applied case definition of 'rickets' are needed to move the field forward.
Disclosure
The authors declared no competing interests.

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P171

Seasonal variations in vitamin D status in children with haematological malignancies in Sweden

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Data on the prevalence of vitamin D deficiency/insufficiency in children with haematological malignancies (HM) in Sweden are scarce. Our studies indicate that one third of children with HM had vitamin deficiency/insufficiency already at the time of diagnosis. In this study, we aimed to investigate the impact of season and age at HM onset on vitamin D status by analysing 25(OH)D levels in two different age groups: children ≤6 years of age, and children >6 years of age. We carried out a cross-sectional study including all 295 children aged <18 years who were diagnosed with HM in our institution between 1990 and 2016 and had a stored serum sample available from the time of diagnosis. All samples had been stored at $-80\,^{\circ}C$. The serum 25(OH)D levels were measured by a direct competitive immunochemiluminescent assay, with reagents from the same batch in January 2018. Serum 25(OH)D levels <25 nmol/L were considered deficient, 25–50 nmol/L insufficient, 50–75 nmol/L sufficient, and ≥75 nmol/L optimal. Clinical data (sex, age, diagnosis, date of the diagnosis) were collected from the Swedish Childhood Cancer Registry. Children ≤6 years old: This group included 163 children (83 males), 3.1% of them had vitamin D deficiency, 20.2% had insufficiency, 44.2% had sufficiency, and 32.5% had optimal levels. Linear regression indicated that season did not influence 25(OH)D levels. Children >6 years old: This group included 132 children (86 males), 10.6% of them had vitamin D deficiency, 34.8% had insufficiency, 34.1% had sufficiency, and 20.5% had optimal levels. When analyzed using unadjusted linear regression, season showed a significant influence on 25(OH)D levels. After adjusting for age and calendar year, season still had a significant impact on vitamin D levels (fall, winter and spring compared with summer, $P=0.046$, $P<0.001$, $P<0.001$ respectively).
Conclusion
Subnormal 25(OH)D levels are common in paediatric patients with HM already at the time of diagnosis, especially in older children. Children >6 years of age had a seasonal variation in levels of 25(OH)D, which was not found in younger children.
Disclosure
The authors declared no competing interests.

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P172

Cow's milk allergic infants on amino acid-based medical nutrition formula maintain adequate serum concentrations of phosphorus, calcium and magnesium despite the use of acid-suppressive medication

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Objectives
We recently demonstrated that cow's milk allergic infants who received an amino acid-based formula (AAF) for 16 weeks as oral feeding had adequate mineral status (1). One factor that may negatively affect mineral solubility and bioavailability and hence mineral status, is high gastric pH (2), but data on this in infants are lacking. Therefore, the present study evaluates serum concentrations of phosphorus, calcium and magnesium in a subgroup of infants on AAF receiving acid-suppressive medication.
Methods
This was a retrospective sub-analysis of a prospective, randomized double-blind controlled study performed between 2008 and 2012 in which infants aged 0–8 months with cow's milk allergy received an AAF (Neocate) either with or without synbiotics (3). Serum concentrations of phosphorus, calcium and magnesium were determined after 16 weeks on AAF ($n=66$) and compared to age-specific reference ranges. Subgroup analysis was performed for infants who were receiving acid-suppressive medication, i.e. proton-pump-inhibitors and H2-antagonists.
Results
Approximately one-third (35%) of the infants received acid-suppressive medication, mainly H2-antagonists. At baseline, mean duration of use was 57 ± 45 days. After 16 weeks on AAF, serum phosphorus, calcium and magnesium concentrations were 1.96 [95%CI: 1.91–2.01], 2.62 [95%CI: 2.59–2.65] and 0.95 [95%CI: 0.94–0.97] mmol/l, respectively and did not significantly differ between users (*P*: 1.95 [95%CI: 1.88–2.03]; Ca: 2.63 [95%CI: 2.59–2.68]; Mg: 0.96 [95%CI: 0.94–0.99]) and non-users (*P*: 1.97 [95%CI: 1.90–2.04]; Ca: 2.61 [95%CI: 2.58–2.65]; Mg: 0.95 [95%CI: 0.92–0.97]) of acid-suppressive medication. None of the infants had mineral concentrations below the reference range.
Conclusion
Although doses, compliance and the neutralizing effect of the acid-suppressive medication were not measured in this subgroup analysis, these data indicate that cow's milk allergic infants orally fed with AAF for 16 weeks maintain target serum concentrations of phosphorus, calcium and magnesium even when receiving these medications. Regular review of the ongoing need for acid-suppressive medication remains recommended.
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P173

Motor and nutritional aspects of individuals with osteogenesis imperfecta assisted in Brazilian midwest region

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Objective
To characterize a group of children with Osteogenesis Imperfecta (OI) followed up at the University Hospital of Brasília (HUB), Brazil.
Methods
Data were collected with children and adolescents that were hospitalized in the HUB for intravenous pamidronate infusion treatment. This hospital is an OI reference center of the Midwest region in Brazil. The sample consisted of thirty-eight subjects, of which 50% were female. 52% of the children had type III of OI, 63.2% of them were diagnosed with OI during the first year of life, and 34.2% had a family history of the disease. The information about the motor aspects was obtained through the application of a questionnaire and the nutritional classification was performed by means of the mass and height evaluation and the BMI was calculated according to the age range recommended by the WHO.
Results
Regarding motor aspects, 42.1% had independent gait, but 78.9% reported not practicing any physical activity. The anthropometric values showed that 27.8% were overweight, 8.3% were obese and 5.6% presented with severe obesity. In the blood sample, 75% were found to have vitamin D levels below the appropriate level.
Conclusion
These data show a general panorama of the OI population assisted in Brazilian Midwest region. Knowing their epidemiological and clinical data on the motor and nutritional aspects may reflect in the best approach to the diagnosis and treatment.
Disclosure
The authors declared no competing interests.
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P174

Supplementation of children with type 1 diabetes with milk or pharmacological calcium for improving bone health – a randomized controlled trial

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Objective
Using DXA, we have previously reported that children with type 1 diabetes (T1D) had short and thin bones (Bone, 2015). Calcium supplementation promotes bone mass accrual with sustained benefit observed using milk/milk-based calcium but not calcium salts. To investigate effect of 1-year supplementation with milk vs pharmacological calcium salt on bone mineral density (BMD) and geometryin Indian underprivileged children with T1D. Both groups received vitamin D supplements.
Methodology
Design: Open label randomized control trial (Pune, India). Children with T1D with disease duration >1yr without co-morbidities were included and randomized to:Group A-1000IU vitamin D+200ml of milk, Group B-1000IU vitamin D+oral calcium carbonate 500 mg/day for 12 months (absorbable calcium $\approx$ 50 mg, both groups). Baseline and endline clinical, diet, physical activity and biochemical data were recorded. Bone mineral content (BMC), BMDand bone geometry were measured using iDXA (Lunar-GE) and pQCT (subset, $n=30$) (XCT2000, Stratec Inc.).
Results
Of 145 children, 136 completed the study. At baseline and endline children were comparable (age-12.3 ± 3.7 yrs vs 12.6 ± 4.1 yrs, HbA1c- 10.5 ± 2.2% vs 10 ± 2% respectively in Group A and B). Sunlight exposure, diet and activity were similar at baseline and endline within and between groups. There was significant improvement in serum calcium, phosphorous, alkaline phosphatase, vitamin D in both groups ($P<0.05$).TBLH BMC, lean mass and THLH BMD increased (percentage increase) by 16.7 ± 16.3 vs 18.6 ± 26.6, 13.2 ± 12.5 vs 13.6 ± 21.2, 8.1 ± 9.9 vs 8.1 ± 10.5 in Group A and B respectively with no significant difference between groups. LS BMAD increased from -0.26 ± 0.03 to 0.28 ± 0.04 in group A and -0.25 ± 0.02 to 0.27 ± 0.04 in Group B, however, there were no differences in percentage increase between groups ($P>0.05$). There was also significant increase in most tibial & radial pQCT based parameters but there were no differences in observed increases in both groups.
Conclusion
Milk and calcium carbonate administered together with vitamin D resulted in increases in both DXA and pQCT measured BMC, BMD and bone geometry, however, there was no difference in increase between the groups. Results of the follow-up study will inform if observed increments in DXA & pQCT measured parameters persist after discontinuation of supplements.
Disclosure
The authors declared no competing interests.
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P175

Dietary behaviours and compromised nutritional intakes in children with Osteogenesis Imperfecta

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Background
Nutrition is a cornerstone of child health. Appropriate nutrient intake contributes to bone health, relevant to conditions of bone fragility. Nutrient intake in chronic conditions can be adversely affected by altered dietary behaviours such as mealtime behaviour and food choice. Dietary behaviour and nutrient intake have not been explored in children with Osteogenesis Imperfecta (OI), the commonest cause of children's bone fragility.
Aim
To pilot assessment of patterns of dietary behaviours and macro- and micronutrient intakes in children with OI.
Methods
Parents of 40 children with OI aged 4–13 years at an OI specialist centre were invited to complete a web-based 4-day food-diary (Intake-24 software), then a web-based questionnaire encompassing 4 tools: Child Eating Behaviour Questionnaire (CEBQ) and Parental Feeding Styles Questionnaire (PFQ1) (scored 1–5: 1 = never – 5 = always), Child Food Preference Questionnaire (CFPQ) (scored 1 = strong dislike – 5 = strong like), and Choosy Eating Questionnaire (CEQ) Intake analysed against Reference Nutrient Intake (RNI) of UK National Dietary Guidance for Children.
Results
Eleven children participated: 5F:6M; Mild-Moderate OI ($n=7$), Severe OI ($n=4$); on bisphosphonate/denosumab ($n=7$); aged 4–6y ($n=3$), 7-10y ($n=5$), 11–13y($n=3$). Intake24 macronutrient analysis showed 100% had above-RNI sugar, with 81% ($n=9$) >4 times RNI. 91% ($n=10$) had carbohydrate intake more than RNI, fat intake was above RNI in 72% ($n=8$). Micronutrient analysis showed 100% had Vitamin D intake markedly below RNI, whereas calcium intake was at or above RNI in 72% ($n=8$). Nine parents completed questionnaires. FEQ showed 66%(6/9) children displayed choosy eating, occurring predominantly in older children (4/6 >7yo). 44% (4/9) offer separate meals, reporting frequent disagreements about food. CFPQ findings included strong preference for sugary-snacks (mean 4.3), dislike of vegetables (mean 2.8). CEBQ scores indicated Food-Fussiness and Emotional Under-Eating in 55% (5/9) 33% (3/9) had Slowness in Eating. PFQ1 showed 100% praise trying new foods, 54% control their child's eating.
Conclusion
Choosy-eating behaviours reported (66%), exceeds background population (8% prevalence in >5yo), with preference for sugary-snacks and reduced preference for vegetables. Impacts were dietary inadequacies across several macro-and micronutrients. Identifying unfavourable dietary behaviours facilitates targeted advice to minimise nutritional compromise in children with OI; important as optimal vitamin D and calcium intake assists bone health.
Disclosure
The authors declared no competing interests.

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P176

Prevalence of vitamin D deficiency in newly diagnosed children with cancer

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Objectives
1) To determine the prevalence of Vitamin D deficiency in children with newly diagnosed cancer; 2) Compare Vitamin D levels of children with and without cancer; 3) Evaluate race and sex differences in Vitamin D levels.
Methods
IRB approved retrospective review of medical records from our pediatric tertiary care center from 2011–2018. Inclusion criteria were serum 25-OH D within 3 months of oncology diagnosis and other non-oncology diagnoses. Exclusions were patients recieving supplemental Vitamin D, and diagnoses and medication use affecting Vitamin D status (e.g. Renal, malabsorption, anticonvulsants). Patients were grouped by race. Oncology patients were age-, race- and sex-matched with three non-oncology patients. Data was analyzed using two-sample t-test for normality, followed by Wilcoxon rank-sum test.
Results
544 patients were included (136 oncology, 408 non-oncology). Mean age was 8.5 years (range 1 month - 19 years). Overall mean 25-OH D level was 22.4 ng/ml in oncology patients and 30.1 in non-oncology patients and was significantly different ($P=<0.0001$). Black patients had the lowest 25-OH D levels in children with both oncology and non-oncology diagnoses, followed by 'other races' (Asian & mixed). The Caucasian children had the best Vit D status, regardless of diagnosis. 22.4% of Caucasian children with cancer had sufficient (30 ng/ml or more) levels, 44.7% were insufficient, and 32.9% were deficient (<20 ng/ml). In contrast, in black oncology patients, 12% were sufficient, 24% were insufficient, and 64% were deficient. This is compared to the non-oncology patients: Caucasian children were 55.3% sufficient, 36.1% insufficient, and 8.6% deficient, and black children were 41.3% sufficient, 28% insufficient, and 30.7% deficient. For all three race categories, differences were seen between races and diagnoses ($P=<0.01$). Black children had the highest rate of deficient levels (64%) compared to the 'other race' category (38.5%) and Caucasian children (32.9%) There was no significant difference in Vit D levels in boys and girls.
Conclusion
Children with cancer have a higher incidence of Vit D deficiency at the time of diagnosis than their non-oncology peers. Physicians should be aware of this risk and consider Vit D testing as a standard practice for newly diagnosed children with cancer.
Disclosure
The authors declared no competing interests.

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P177

Feasibility of a 13-week targeted exercise intervention on tibial bone mineral density in adolescents with Developmental Coordination Disorder

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Objectives
Adolescents with Developmental Coordination Disorder (DCD) have significantly lower bone mineral density (BMD) compared to their non-affected peers. Their difficulty in performing weight bearing movement skills is hypothesised to explain poorer bone characteristics. This feasibility study examined the impact of a 13-week exercise intervention on tibial bone parameters in adolescents with DCD.
Methods
Twenty-eight adolescents with DCD participated in a 13-week intervention of cardiorespiratory, strength and resistance exercises for 90 minutes, twice per week. Lower limb bone parameters and fitness tests were measured pre- and post-intervention. Bone parameters included proximal (66%) and distal (4%) sites of the non-dominant tibia (T66 and T4) using peripheral Quantitative Computed Tomography. Fitness tests included the 1 Repetition Maximum leg press, vertical jump and standing broad jump. Paired sample t-tests (or Wilcoxon signed-rank test) examined pre-post differences. Generalised estimating Default (GEE) evaluated pre-post intervention changes whilst controlling for gender, pubertal stage, age, number of sessions attended and body mass index.
Results
Adolescents, 17 boys and 11 girls, aged 12.6 years to 17.6 years ($M=14.06$, SD = 1.28 years) were mid ($n=14$) or post ($n=12$) pubertal stages; ($n=2$ pre-pubertal). Significant increases post intervention were present for T66 mass ($t(27)=2.75$, $P=0.010$, $d=0.23$), T66 cortical area ($Z=2.45$, $P=0.014$, $d=0.23$), 1RM leg press ($Z=2.78$, $P=0.005$, $d=0.53$), standing broad jump ($t(27)=2.74$, $P=0.011$, $d=0.15$) and BMI ($t(27)=2.30$ $P=0.029$, $d=0.10$). GEE models for T66 mass and cortical area, found these changes were significantly associated with the number of sessions attended, in addition to vertical jump and standing broad jump measures.
Conclusion
Results suggest that for adolescents with DCD some bone parameters in the lower leg can respond to targeted bone loading exercise and improve, despite the short 13-week intervention and small effect sizes. Considering that effects of bone

adaptation may not be fully appreciated in this short time, targeted exercise focussed on loading the lower limbs can improve bone health outcomes in this group. Further studies with a control group, larger sample and over a longer period of time are required to confirm positive changes to bone health, and determine whether optimal BMD scores similar to their non-affected peers can be achieved.

Disclosure

The authors declared no competing interests.

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P178

The role of hydrotherapy in the management of children with severe Osteogenesis Imperfecta

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Background

Osteogenesis Imperfecta (OI) is most commonly caused by a defect in the genes which produce type 1 collagen. Features of OI include fractures, hypermobility and weakness. Severely affected children can present with deformities such as bowing of long bones and spinal curves. Mobility may be significantly impaired. The medical management of children with severe OI includes orthopaedic surgery and bisphosphonate treatment. Physiotherapy to promote function and participation is central to their overall management. This includes facilitating motor development, strengthening and rehabilitation post fracture or surgery. Some severely affected children struggle with land-based physiotherapy due to the extent of their bone fragility, weakness, or limitations caused by the shape of their bones.

Clinical management

Hydrotherapy, therapeutic exercise in water, is regularly used by the physiotherapy team at a highly specialised centre for paediatric OI. The aim of this poster is to demonstrate the effectiveness of hydrotherapy in the management of children with severe OI, illustrated by three case examples. Three children, aged eleven months, four years and seven years, attended six sessions of hydrotherapy. Sessions were led by a physiotherapist experienced in OI. Parents were invited to take part in sessions. Child focused goal-setting was used to assess effectiveness, and parent experience was recorded.

Discussion

Hydrotherapy enabled an eleven month old with marked limb bowing and gross motor delay to achieve positions he was initially unable to achieve on land. Parental confidence increased when handling their child. Hydrotherapy introduced a non-ambulant four year old to graded weight-bearing activities following bilateral rodding surgery, enabling progression to land-based gait re-education. Land based therapy was limited for a child aged seven years, due to his fragility, weakness and severe kyphoscoliosis. Hydrotherapy enabled him freedom of movement, muscle resistance training and an opportunity to improve his cardiovascular fitness. All parents reported that hydrotherapy was very important in their child's overall management and that their child had benefited significantly from sessions. These three case examples illustrate that hydrotherapy is a valuable and effective therapy adjunct for the physiotherapy management of children with severe OI. Its benefits for the child and family are numerous and versatile.

Disclosure

The authors declared no competing interests.

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P179

Clinical and radiological characteristics of children's forearm deformations with hereditary multiple exostosis (Clinical observation)

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Objectives

Frequency of occurrence of forearm deformations developed against the background of a hereditary multiple exostosis (HME) in children reaches 30–80%. The clinical and radiological data of forearm deformities have not been sufficiently researched yet. The purpose of our research is specification of children's forearm deformities developed against the background of HME.

Methods

Retrospectively and prospectively we selected and analyzed 100 patients with the diagnosis 'Hereditary Multiple Exostosis' aged from 2 till 17 years. The assessment of forearm deformations was carried out on the basis of clinical and X-ray methods of research according to reference lines and corners for forearm bones.

Results

It has been revealed that in 100% of the cases functional restrictions and cosmetic defect of forearm take place. Complaints about a pain syndrome were registered in 20% of the cases. We revealed the most often forearm deformations, which be classified as ulna deformities and radius deformities, they include: varus and recurvation of ulna on border of the top and average third (65%); varus of ulna in the average third (9%). As for radius deformities, they include: varus of radius in the average third (20%); varus of radius in the lower third (6%). Both ulna and radius deformities are accompanied with shortening of bones of the forearm (in 100% of the cases) and subluxation or dislocation of the radial head (30%).

Conclusion

The variety of children's forearm deformations developed against the background of HME implies differentiated approach to the choice of individual techniques of surgical treatment in each case.

Disclosure

The authors declared no competing interests.

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P180

A retrospective review of modern spine surgery in the skeletal dysplasia population

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Objective

Existing case series examining outcomes following spine surgery for patients with skeletal dysplasias demonstrate high rates of complications. Yet, these earlier studies are from a single institution, contain surgeries performed almost 50 years ago, and only include patients with a diagnosis of achondroplasia. The objective is to determine contemporary outcomes after spinal surgery in patients with skeletal dypslasias, focusing on complications and revisions. We predict that advancements in spine surgical techniques should result in lower rates of complications and revisions in patients with skeletal dysplasias.

Methods

37 consecutive patients who underwent spinal surgery between 2007 and 2017 were identified from our skeletal dysplasia registry. A chart review was conducted to determine patient demographics, medical/surgical history, surgical diagnoses, complications, and revision surgeries. Seven patients were excluded due to incomplete data, leaving 30 patients available for inclusion. Charlson comorbidity indices were calculated as a composite measure of overall health.

Results

Achondroplasia was the most common skeletal dysplasia (67%) followed by spondyloepiphyseal dysplasia (20%) and diastrophic dysplasia (7%). Average age of the cohort was 40 (range 6–75), and the majority of patients were in excellent health (60% Charlson Comorbidity Index .1). Indications for surgery ranged from cauda equina syndrome to symptomatic osteochondroma. The most commonly performed surgery was a multilevel thoracolumbar decompression without fusion (57%). The overall rate of complications was high: durotomy (37%), infection (13%), and neurologic complication (10%). Seven patients (23%) required revision surgery and four patients (13%) required extension of a previous decompression due to ongoing symptoms. No patient was revised for instability.

Conclusion

Surgical complication rates following spine surgery remain high in many forms of skeletal dysplasias, even with modern surgical techniques. Medical complications have decreased, likely due to improved perioperative care and may also reflect better care in the pediatric years. Revisions and extensions for persistent stenosis are common.

Disclosure

Advisory Board or Panel. Alexion – Speaker's Bureau. Ascendis – Advisory Board or Panel.

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P181

Walking quality of children with healed Perthes disease

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Objectives
Children with Perthes disease may present with altered walking patterns even at the healed stage of the disease. The aim of the study was to assess the walking endurance, fatiguability and gait changes of children with healed Perthes disease, and to determine if walking endurance is associated with hip function and quality of life.
Methods
Fifty-one children (38 males) aged 8–16 years with >3 years post-diagnosis of Perthes disease completed this cross-sectional study. Normative data was extracted from a contemporary Australian data set (1000 Norms Project) including 152 similarly aged children (76 males). Walking endurance was assessed with the six minute walk test (6MWT) with temporo-spatial gait parameters recorded throughout by the GAITRite system. The Non-arthritic hip score (NAHS) and Global Paediatric Outcomes Data Collection Instrument (PODCI) were also completed.
Results
In comparison to healthy peers, children with healed Perthes disease exhibited significantly reduced walking endurance (6MWT mean difference 181.2 m, 95% CI 152.4 – 210, $P<0.01$). No fatiguability was seen during the 6MWT with no significant difference observed between the distance covered in the first and last minute (mean difference 0.05 m, 95% CI −6.19 – −6.29 m, $P=0.98$) or the cumulative distance between the first three and last three minutes (mean difference 1.94 m, 95% CI −12.6 – 16.48 m, $P=0.49$). Children with unilateral disease ($n=43$) walked significantly faster (mean difference 0.14 m/s, 95% CI 0.07 – 0.21 m/s, $P<0.01$) with a higher cadence (mean difference 9.3 steps/min, 95% CI 1.1 – 17.4 steps/min, $P<0.01$) compared to children with bilateral disease ($n=8$). Overall, children with Perthes disease reported excellent hip and global function (NAHS mean score 94.4/100; PODCI mean score 90.7/100), with higher scores moderately correlated with greater walking distances ($r^2=0.46$ – 0.49, all $P<0.01$).
Conclusion
Children with Perthes disease have reduced overall walking endurance in comparison to healthy peers. However, they perceive their hip function to be high. Although gait fatiguability was not established during the 6MWT, children with bilateral involvement demonstrated an altered gait strategy to children with unilateral disease. Walking endurance and quality should be considered in the long term outcome assessment of the management of Perthes disease.
Disclosure
The authors declared no competing interests.

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P182

Handgrip strength as functionality and independence indicative in Osteogenesis Imperfecta

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Objectives
This study aimed to correlate handgrip strength and functionality of children with Osteogenesis Imperfecta (OI).
Methods
Thirty-eight children and adolescents with different types of OI were single-timed evaluated during their hospitalization for pamidronate intravenous infusion at the University Hospital of Brasília, Brazil. This hospital is the Brazilian Midwest reference for OI treatment through the national health system. These children were 8.21($\pm$4.26) years of age; 50% were girls ($n=19$); most of them (52.6%) had OI type III diagnosis. They were assessed three times with a manual dynamometer for handgrip strength of the hand free of medication and the authors considered the average score of those three trials. The parents were questioned about their child's functionality and autonomy through the Pediatric Evaluation of Disability Inventory (PEDI), that measures the capability and performance of functional activities in three content domains: self-care, mobility and social function.
Results
Handgrip strength in these children and adolescents ranged from 3 to 33 kgF and PEDI scores ranged from 2 to 64 points. We observed a positive, significant ($P=0.032$) and regular ($r=0.457$) Spearman's correlation between PEDI values and the average of handgrip strength of these children.
Conclusion
Children and adolescents that are most functional and independent had greater scores at PEDI evaluation and this correlates with handgrip strength observed through manual dynamometer. This may be a simple and quick measure to infer the functionality and independence of these patients in a hospital environment.
Disclosure
The authors declared no competing interests.

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P183

Functional outcomes of an adult with Osteogenesis Imperfecta after rehabilitation post-bilateral Girdlestone procedure: a case report

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Osteogenesis imperfecta is a disorder characterized by bone fragility. Current management includes the usage of bisphosphonates to improve bone stock and manage pain. Outcomes in adults have mainly been reported in terms of presentation compared to genotype, most probably due to the heterogeneity of the disease. The head and neck resection of the femur, or Girdlestone procedure, was a common procedure to treat infections of the hip but it has fallen out of favor due to the advent of hip replacements, and its use has been limited to a last resort. Functional outcomes and patient satisfaction have been reported in small samples of unilateral Girdlestone arthroplasty; however, the bilateral application of the procedure has remained anecdotal thus far, and is of novel use in a patient with osteogenesis imperfecta. Through the efforts of physiatrists, geneticists and orthopedic surgeons, with the use of rehabilitation management, pharmaceutical interventions in the form of bisphosphonates, and well planned surgical approaches, the patient was able to achieve pain-free sitting, independent transitions, and short-distance ambulation. These functional improvements have allowed the patient to care for herself more effectively and return to her work as a municipal accountant. The outcome measures taken quantitatively measure the patient's improvement and provide guidance as to which areas need more focus, particularly in terms of interventions for fracture prevention and improvement of balance. The outcome measures also place the patient in the context of other cases worldwide, highlighting their differences in terms of physical attributes, and similarities in terms of their functional attainment.
Disclosure
The authors declared no competing interests.

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P184

Material based on bioactive glass to replace bone defects in children after removal of tumors

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Objectives
Orthopedics use many different biological grafts, organic, inorganic and synthetic materials to replace residual bone defects. Recently, materials based on bioactive glass, which have a more effective osteostimulating factor, are being actively studied.
Methods
Bioactive glass based material is a multiphase inorganic material synthesized by chemical deposition and ceramic technology, having osteoinductive and

osteoconductive properties, quickly integrates with the bone and transforms into bone over time. Bone-plastic surgery using bioactive glass was performed on 92 children with benign bone tumors. The material was applied in the form of granules or powder.
Results
As a result of osteoplastic operations, no complications from the postoperative wound were found. Tumor recurrences were detected in 8 (8.7%) patients. In the course of X-ray monitoring, restructuring and replacement of plastic material with newly formed bone tissue was observed. The patients used the operated limb after an average of 3–6 months.
Conclusion
The use of a material based on bioactive glass during osteoplastic operations has a number of advantages – the volume and time of operation decreases, stimulation of bone reparative osteogenesis occurs, which contributes to the restoration of bone structure and limb function.
Keywords
Bioactive glass, benign bone tumors, children.
Disclosure
The authors declared no competing interests.
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P185

High impact exercise to improve musculoskeletal outcomes in Crohn's disease: a feasibility questionnaire

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Objective
Bone and muscle deficits are observed in patients with Crohn's disease (CD). High-impact exercise (HIE), such as jumping based exercise, can provide hypertrophic and osteogenic stimulus, however to date there have been no studies of HIE in CD. This study aimed to assess the acceptability and feasibility of participating in HIE in adolescents and adults with CD.
Methods
Two anonymous questionnaires surveyed adolescents and adults, respectively, with CD. These questionnaires assessed patients' exercise habits and how this relates to disease symptoms and status; acceptability of participating in HIE; perceived difficulty of participation in HIE based on a short video demonstration; and intentions towards participating in future research studies of HIE in CD.
Results
Forty-eight (22 adolescents [68% male], 26 adults [50% male]) CD patients with median age 19 years (13 to 40) completed this survey. Overall disease status was rated as good, and general wellbeing was primarily 'very well' (52%), or 'slightly below average' (38%). Fifty-six percent said CD makes exercising difficult, mainly due to fatigue (78%) or joint paint (56%). Positive benefits of exercise included improved mood (77%), feelings of strength and fitness (56%) and increased energy levels (31%). Exercise exacerbated feelings of fatigue and joint pain in 44% and 31%, respectively. Exercise did not exacerbate any CD symptoms in 38% of patients. The majority were positive towards exercise, with 65% stating they could exercise ≥ 3 times per week. Forty-four percent were not concerned about their bone health, with 46% and 10% slightly and very concerned, respectively. Despite this, 98% believed the opportunity to improve bone health was worth participating in HIE three times per week. Attitudes towards participating in future HIE research studies were positive, with 83% respondents stating they would be interested in taking part. Perceived difficulty of HIE was low, and was positively associated with disease control ($r=0.35$; $P=0.02$), and general wellbeing ($r=0.66$; $P<0.001$).
Conclusion
Despite limited concern for bone health, attitudes towards exploring HIE as adjunctive therapy in CD patients were positive, warranting the development of future research studies to establish the safety and efficacy of HIE.
Disclosure
Richard K Russell has received speaker's fees, travel support, or has performed consultancy work with: Nestlé, AbbVie, Takeda, Napp, Mead Johnson, Nutricia and Janssen. Dr Daniel R Gaya has received travel grants and speaker honoraria from Vifor, Ferring, Pfizer, Abbvie, Takeda & Janssen.
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P186

Severe osteoporosis with life threatening vertebral fractures in a 15-years-old boy with juvenile idiopathic arthritis: a successful spinal cord decompression and posterior spinal fusion Th2-Th12

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Background
Chronic rheumatic conditions including juvenile idiopathic arthritis (JIA) lead to the deterioration of bone mineral metabolism and confers risk of fragility fractures. Although contemporary medical therapies have limited skeletal complications in JIA, some rare cases of severe osteoporosis are still reported in these patients. Systemic glucocorticoid (GCS), long-term inflammation, and disease-related immobility are responsible to skeletal damage in JIA.
Presenting problem
We discuss a case of a 15-year-old boy treated for 13 years due to systemic onset JIA. Diagnosed at 2nd year of life, henceforward he presented with severe polyarticular involvement (>30 joints affected), limited range of movement, short stature, and muscle atrophy. The immunosuppressant therapies included methotrexate, cyclosporine, and TNF-alpha inhibitors. The patient required continuous treatment with oral and/or intravenous GCS, and subsequently developed glucocorticoid-dependence with apparent clinical manifestations of GCS adversity. Both clinical and densitometric signs of osteoporosis were found. The DXA scan showed: Lumbar BMD Z-score $=-4.3$; Femoral BMD Z-score $=-5.7$. Despite pamidronate therapy, evident vertebral compression fractures Th4, Th7, Th9 and L1 were found on MRI scans. The patient sustained a sudden, unexpected critical spinal cord compression resulting in lower body palsy, diplegia, severe neurological damage, and neurogenic urinary bladder.
Clinical management
Due to the rapid progression of the neurological damage, and serious sequence of the process, the patient was referred to prompt orthopedic and neurosurgical emergency. He was then successfully treated using a unique high-risk surgery in a specialized centre. A fast-track procedure was performed as a matter of urgency: the spinal cord decompression was effectively carried out, accompanied by a large posterior spinal fusion Th2-Th12.
Discussion
This is a report of an exceptional orthopedic surgery performed on the osteoporotic bone in the spine. The above case demonstrates that the risk of life threatening osteoporosis should still be considered during the chronic course of juvenile arthritis in pediatric patients, and, furthermore, a multidisciplinary comprehensive approach is necessary. The glucocorticoid-induced osteoporosis is one of the most serious complications of the rheumatic diseases in children, and should always be taken into account, even in the era of modern treatment.
Disclosure
The authors declared no competing interests.
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P187

Increased prevalence of overweight and obesity and its clinical predictors in children affected by X-linked hypophosphatemia

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Background/aim
X-linked hypophosphatemia (XLH) is a rare disease characterized by low phosphate level. Scientific evidence points to link between hypophosphatemia and obesity in general population. The aim of our longitudinal observational study was to investigate the prevalence of obesity and associated factors in a large cohort of children with XLH.
Patients/methods
We selected 172 XLH-children of 5–20 years (113 girls/59 boys). Anthropometric parameters (weight, height, BMI) were collected at birth and during follow-up at mean age of 5.3–8.2–11.3–15.9 years (group 1–2–3–4, respectively). In each group, subjects were classified based on International Obesity Taskforce (IOTF) cut off values of BMI for age and sex as overweight or obese (IOTF 25–30 or ≥ 30 kg/m^2, respectively).
Results
In each age-group, almost 1/3 of XLH-patients were classified as overweight/-obese (29.4% vs 28.7% vs 27.5% vs 36.7% for group 1–2–3–4, respectively). Children without XLH-family history had significantly higher BMI-IOTF at every point of follow-up ($P=0.015$), compared to those with positive XLH-family history. Similarly, higher BMI-IOTF is significantly associated with treatment duration (23.3 ± 4.4 vs 23.8 ± 3.8 vs 25.2 ± 4.5 kg/m^2, for subjects with treatment duration of <5, 5–10 and >10 years, respectively, P for trend $=0.025$). Multiple regression analysis confirmed that treatment length and lack of XLH-family history are positively associated with higher BMI-IOTF.
Conclusion
1/3 of XLH-children have phenotypically unfavourable metabolic profile expressed as increased prevalence of overweight/obesity in comparison to general population. Lack of XLH family history and length of treatment increase the risk of higher BMI-IOTF. BMI should be carefully followed in children, and later adults, with XLH.
Disclosure
The authors declared no competing interests.
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P188

Impact of type 1 diabetes mellitus on skeletal integrity and strength in adolescents aged 12 to 16 years; as assessed by High Resolution peripheral Quantitative Computed Tomography (HRpQCT)
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Objectives
To investigate the impact of Type 1 Diabetes Mellitus (T1DM) on cortical and trabecular microarchitecture, and bone strength in adolescents; using High Resolution peripheral Quantitative Computed Tomography (HRpQCT) and microfinite element analysis. To our knowledge, this is the first study in children, assessing the impact of T1DM on skeletal microstructure and strength using HRpQCT.
Methods
We recruited 22 patients aged 12–16 years with T1DM who were matched by age and gender with healthy controls. Recruits underwent a standard medical and fracture history; and diabetic therapy and control was assessed in T1DM patients. Participants then underwent DXA and HRpQCT scans. Paired *t*-tests were applied to assess differences in total body, lumbar and pelvic DXA parameters, cortical and trabecular microstructural parameters and skeletal strength. Regression analysis was used to determine if there was an association between HbA1C and duration of diabetes with changes in cortical and trabecular microarchitecture, and bone strength.
Results
There was no significant difference in the total body, lumbar spine and pelvic bone mineral density. Tibial trabecular thickness was lower in T1DM patients (-0.005 mm; CI -0.01, -0.001, $P=0.029$). There was a reduction in trabecular loading at the distal radius (Tb.F/TF distal: -6.2; CI -12.4, -0.03, $P=0.049$) ,and distal and proximal tibia (Tb.F/TF distal: -5.2; CI -9.2, -1.2, $P=0.013$), (Tb.F/TF proximal: -5.0; CI -9.8, -0.1, $P=0.047$). Regression models demonstrated a reduction in tibial stiffness (-0.877 kN.mm, $P=0.03$) and tibial failure load (-0.044 kN, $P=0.03$) with higher HbA1C before and after adjusting for age and gender.
Conclusion
Alteration of tibial trabecular microarchitecture is associated with an alteration in tibial loading properties. Similar loading alterations at the radius also appear to emerge in children with T1DM. Poor diabetic control may contribute to reduced tibial bone strength. Larger patient cohorts are required to determine if T1DM results in changes in skeletal integrity driven by duration and control of T1DM in childhood.
Disclosure
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P189

Cleidocranial dysplasia: a patient with severe dental phenotype
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Background
Cleidocranial dysplasia (CCD) is an ultra-rare (1/1,000,000) genetic bone disorder, characterized by hypoplastic or aplastic clavicles, persistence of wide-open fontanelles and multiple dental abnormalities. It is caused by mutations in the RUNX2 gene, involved in the differentiation of osteoblasts.
Presenting Problem
A case of a 13 year-old girl with a clinical diagnosis of CCD is reported. Her clavicles were hypoplastic and her shoulders could be approximated anteriorly. Her fontanelles closed at the age of three years and she had severe dental health issues, including an operation of the left mandible to remove a supernumerary tooth. The presenting complaint was the presence of 'clicky knees'.
Clinical management
Full bone health evaluation, work up for comorbidities and comprehensive dental assessement were performed. She had short trunk, scoliosis, pes planus and genu valgum, small thorax, hyperextension of knee and elbow joints and numerous naevi. Her bone mineral density was low-normal and the basic laboratory bone profile was unremarkable. The main imaging findings were: wormian bones of the skull, hypoplastic clavicles, osteopenia, cone-shaped thorax, slender bones and wide pubic symphysis. Her audiogram was normal, as was her cognition. Her dental assessment revealed crowded mixed dentition, moderate dental hygiene, dental caries and absence of the lower right lateral incisor. Her orthopantomography showed supernumerary teeth on the right mandible and a two-years delay of her dental age. Her dental treatment plan includes restorations of the caries lesions, orthodontic treatment, surgical removal of the supernumerary teeth to allow eruption of the permanent ones and recalls every 3–4 months. Advice was also given on vaccinations, exercise and physiotherapy for muscle strengthening and healthy diet. A genetic test for confirmation of the clinical diagnosis is being scheduled and she is being reviewed on an annual basis.
Discussion
The effective management of the dental anomalies is very important for CCD patients and focuses on achievement of optimal function and aesthetics. What is equally crucial is the comprehensive and regular skeletal assessment, given that RUNX2 plays an important role in bone formation. Finally, detailed surveillance for complications such as deafness, growth failure and recurrent respiratory infections is necessary.
Disclosure
The authors declared no competing interests.
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P190

Cone-shaped epiphyses involving the knees: report of a case and differential diagnosis
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Background
Metaphyseal chondrodysplasias with cone-shaped epiphyses and cup-shaped metaphyses are very rare. We present a case with this particular skeletal phenotype, along with its differentials.
Presenting Problem
Our female patient, aged 3.8 years, was the 2nd child of healthy, unrelated Greek parents, who were worried about her bilateral knee stiffness, which resulted in a

limp and also in walking with her knees bent. At presentation, she was noted to have short stature, internal rotation of the left leg and lordosis. She was otherwise normal on examination and not dysmorphic.
Clinical management
A comprehensive orthopaedic review and a full endocrine work up were undertaken. Her biochemical profile, including bone metabolism, was normal. Her X-rays of the lower limbs from the level of the knee joints to the ankles demonstrate major deformities. The distal metaphyses of the femurs and proximal metaphyses of the tibiae are enlarged and deepened, becoming cup-shaped by enlarged and cone-shaped epiphyses. Least marked changes are also present in the distal end of the tibiae. Her upper limbs and spine X-rays were normal.
Discussion
The main differentials of the isolated cone-shaped epiphyses at the knees include rare disorders such as trichoscyphodysplasia (which also includes facial dysmorphism and ectodermal dysplasia) and acroscyphodysplasia (which is accompanied by brachydactyly and psychomotor delay). In addition, it has been described in cases of vitamin C deficiency and hypervitaminosis A. None of the above features was present in our case. Lastly, this rare entity has been characterized as redisual deformity after meningococcemia. Interestingly, our patient had a history of neonatal septicaemia (due to Klebsiella Pneumoniae and Serratia Marcescensis) and this event could possibly (and by exclusion) be related to her dinstict skeletal phenotype.
Disclosure
The authors declared no competing interests.
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P191

Supporting the emotional well-being of children living with osteogenesis imperfecta; an upstream health promotion initiative
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Background
Sheffield Children's NHS Foundation Trust offers a highly specialised metabolic bone service for children and young people living with Osteogenesis Imperfecta (OI). OI is a chronic health condition causing bone fragility, bone pain, bone deformity, frequent fractures and variable physical limitations with wide reaching consequences on both children and families; the potential to experience elevated psychological distress is common.
Presenting problem
The worldwide prevalence of children living with a chronic physical condition and requiring long term management is estimated at around 25%. Chronic physical health conditions are associated with low mood, depression and anxiety with a concomitant decline in psychosocial outcomes such as academic performance, self-esteem and quality of life. Compared to their non-disabled peers these children are more susceptible to social/emotional difficulties; as many as half are estimated to meet the criteria for a diagnosable mental health condition. There is increasing evidence that better physical and mental health outcomes are achieved when both are factored into treatment and management of long term conditions such as OI.
Management
This poster describes an innovative health promotion initiative to strengthen the emotional well-being of children and families living with OI. The resource, a leaflet presented in both digital and paper format, offers information to parents/carers and teachers to enable them to develop the skills to promote resilience, self-efficacy, self-esteem and coping strategies. The resource adheres to the psychological principles of learning. It provides information and understanding on developmentally appropriate worries and fears, commentary and insight into attitudes and beliefs often experienced by children and parents/carers, and teaches skills and competencies from Cognitive Behavioural Therapy (CBT) and Acceptance and Commitment Therapy (ACT) to strengthen emotional well-being.
Discussion
Whilst health promotion resources may not substitute 1:1 education and advice,when supplemented with a designated OI service and targeted interventions, there is the potential for an 'upstream' mental health promotion initiative to bring about substantive change in the often complex behaviours seen in children and families living with OI. Feedback from allied health professionals, academics, families living with OI and charities working with this group, suggests the resource can be effective in meeting this need.
Disclosure
The authors declared no competing interests.
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P192

Developing a high chair to meet the needs of infants with Achondroplasia; a collaboration between Evelina London Children's Hospital and Brunel University
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Achondroplasia is the commonest form of dwarfism. Key features in infancy impacting positioning are rhizomelia, spinal deformities and large head size. Both standard high chairs and specialized adaptive seating are currently inadequate to meet the needs of these infants. This is due to their anatomical limitations and the guidance for supportive positioning in this group of children, which recommend that a flat, elongated spine is optimal, avoiding a 'C shape', as is a 45 degree recline from upright when in a seated position (Shirley & Ain 2009). We present a unique and innovative collaboration between the Evelina London Children's Hospital and the Brunel University Product Design degree programme, to develop a high chair to meet the specific needs of infants with achondroplasia.
Notable design features include:

- Adjustable seat depth (to accommodate rhizomelia)
- Recline adjustment up to 30–45 degrees from upright position (to follow spinal management recommendations)
- Headrest to be incorporated (to support head control)

It was considered important for the seating to be aesthetically pleasing and socially acceptable as a piece of furniture in the home. After initial development, the prototype was trialed with parents and infants in the multidisciplinary achondroplasia clinic and presented at the Restricted Growth Association (RGA) 'Big Weekend'. Parent feedback has been sought at every stage, fundamentally influencing the design process. Parents reported positive aspects including the overall design concept and size. They also suggested improvements e.g. using a five-point harness and shoulder supports. Parent feedback from 'road-testing' has led to final modifications being made, such that commercial partners are being sought for further development. Whilst the high chair has been designed specifically for children with achondroplasia to provide seating for feeding, from weaning until approximately 2 years of age, it may also be utilised by children with other skeletal dysplasia conditions where seating options may be similarly limited.
Disclosure
The authors declared no competing interests.
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P193

Double trouble: A case of trisomy 21 and achondroplasia
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Background
The co-occurrence of achondroplasia with Trisomy 21 is extremely rare, with only a handful of published case reports in the literature.
Presenting Problem
A baby girl had an antenatal diagnosis of incomplete atrioventricular septal defect (AVSD), and a subsequent postnatal diagnosis of Trisomy 21. At birth she had respiratory distress and required CPAP until 5 days of life. AVSD was confirmed on postnatal ECHO. Phenotypic traits consistent with Trisomy 21 were noted, and confirmed on karyotype. She was discharged home on day eight. In neonatal follow up clinic at 7 weeks old she was noted to have a relatively large head (OFC on the 90th centile compared to weight and length which were on the 9th and 20th centile respectively) right sided plagiocephaly, short limbs with rhizomelic shortening, trident hands and a lumbar gibbus.
Clinical management
Skeletal X-rays showed shortening of the long bones, especially femur and humerus, squared iliac bones and narrow sacrosciatic notches, in keeping with a diagnosis of achondroplasia. Further genetic tests confirmed the diagnosis of achondroplasia. Health surveillance for each condition is different. Specific airway issues arise with both conditions which was especially important for this baby who required intubation and ventilation for cardiac surgery. Specific handling advice is required for infants with achondroplasia due to a large head, and this was vital due to her hypotonia. The multi-disciplinary team approach with specialist OT input has been helpful in the ongoing management of this patient.

Discussion
The presence of Trisomy 21 and achondroplasia in the same patient is rare. The first case was published in 1970 and to date there are only seven published case reports. Both conditions have distinguishable phenotypic features which are relatively commonly seen in paediatrics. Disease specific health surveillance is required, and has increased significance when these two conditions occur together. Disease specific multidisciplinary input was key in optimizing her clinical care.
Disclosure
The authors declared no competing interests.
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P194

Skeletal dysplasia in Saul Wilson syndrome
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Background
Since Microcephalic osteoplasic dysplasia; Saul Wilson Syndrome (SWS) was first reported by Saul and Wilson in 1990 only 14 cases have been reported worldwide. In 2018 Ferreira et al identified the pathophysiological mechanism for SWS as a recurrent De Novo Heterozygous COG4 Substitution.
Objective
To describe the diagnostic process in a case of SWS.
Presenting problem
The patient is the first-born child of healthy, non-consanguineous parents. Pregnancy and delivery was normal with birth weight and length within normal limits for GA. After birth he presented with severe failure to thrive. His anterior fontanelle was large and extended to the dorsum nasi at birth. At 4 months he had an aventricular peritoneal shunt on clinical indication. He presented with dysmorphic craniofacial features: low set ears, small dysplastic face with micrognathia, and narrow nasal bridge, contractures of the elbow and knees, clubfoot and short distal phalanges. In the beginning his speech development was impaired. He is hearing impaired and ocular findings are blue sclerae, prominent eyes and cataracts. The MRI showed delayed myelination, hypoplasia of corpus callosum, small cysts in capsula interna and anterior displacement of atlas with abnormal course of the proximal cervical medulla and pons. The 3D CT of the cranium showed open sutures, delayed ossification and an abnormal spine with shortened vertebra and subluxation.
Clinical management
The patient had several investigations performed without finding the diagnosis: Array CGH, conventional chromosomes and X-ray of whole skeleton. At the age of three a splenectomy was performed due to an enlarged spleen, anaemia and thrombocytopenia. The patient is neutropenic and prone to infections. Due to two severe femur fractures treatment with bisphosphonate and zoledronic acid was initiated. The diagnosis was made, when the patient was 10 years old, after a photo of a patient with similar dysmorphic features was discovered and WES showed the patient to be heterozygous for c.1546G>A, p.Gly516Arg in the COG4-gene. The treatment of SWS is symptomatic and patients have lived in to adulthood.
Conclusion
This case shows how important collaboration between clinicians and scientists are in dealing with and diagnosing very rare cases of bone dysplasia.
Disclosure
The authors declared no competing interests.
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P195

Growth velocity measured by biomarker, COLX, in Achondroplasia
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Objectives
Achondroplasia (ACH), caused by a mutation in the fibroblast growth factor receptor 3 gene (FGFR3), leads to inhibition of endochondral bone growth. Three potential treatments all targeting the FGFR3 on different levels of the pathway are under development. To compare the different approaches there is a need for precise measurements of efficacy. COLX and other biomarkers of bone growth are biological by-products of endochondral bone growth. A nationwide study of ACH children age 2–15 years is conducted evaluate the use of biomarkers as an indicator of short term bone growth.
Methods
15 ACH children completed more than $\geq$6 months of growth measurements in an observational study. Growth velocity was evaluated by anthropometric measurements (arm-span, sitting and standing height) and blood samples were collected every 3 months for analysis of biomarkers reflecting bone turnover. The ACH children were compared to a healthy cohort with normal growth (n = 194, 99 females, 95 males, range: 6.7–16.8 years). We aim to establish reference ranges for CXM in healthy children, to evaluate CXM in relation to age, sex, puberty and peak height velocity and in relation to other biomarkers of bone growth.
Results and Conclusion
Data from the initial 3 months of follow-up in ACH group is compared to the control group. Data analysis will demonstrate the potential of biomarkers as sensitive indicators of growth velocity and as indicators of efficacy in developing new treatments for ACH. Reference ranges using GAMLSS statistical approach will be constructed for age and sex-dependent SD-score for COLX and data for the ACH is plotted against the children with normal growth.
Disclosure
The authors declared no competing interests.
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P196

Sleep related problems in children with osteogenesis imperfecta
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Osteogenesis Imperfecta (OI) is a genetic disorder affecting 1 in 10,000 births with a wide variability in phenotypes. Clinical Manifestations include; recurrent fractures, bone pain, varying degrees of short stature and deformity, scoliosis, kyphosis, and respiratory failure in the severest types. Sleep disorders are under-acknowledged and are often more problematic in children with chronic illnesses. Moldosky[1] identified the link between pain affecting quality of sleep, suggesting that lack of sleep contributes to the pain itself. Children with OI may also be likely to complain of poor sleep quality due to night sweats, structural changes in the chest and spine restricting the lungs, and changes in soft tissues leading to decreased muscle tone, which may be linked to obstructive sleep apnoea.
Objectives
Gain an understanding of sleep related problems in OI. Understand whether sleep related problems are a significant issue within our patient cohort which require more routine assessment and management.
Methods
Patient and carer questionnaires.
Results
55 patients and their parent/carer completed the questionnaires during routine admission or outpatient appointment. The patient cohort included 26 females, age range 3.1 to 17.3 years, mean age 12.77. The group varied in terms of the type of OI; 32 mild, 13 moderate, 10 severe. More than half of the patients questioned (67%) reported difficulty in getting off to sleep. 36.4% of participants reported waking in the night, with discomfort (44%) and feeling too hot (36%) being the most common causes. Frequency of night time waking ranged from 0–4 times a night. Over half the participants reported snoring.
Conclusions
This service evaluation has highlighted a large proportion of OI patients have issues related to sleep; difficulty settling to sleep; night time waking and difficulty getting up in the morning. A pilot study on a small sample of OI patients is ongoing, examining the feasibility of full polysomnography sleep studies, alongside sleep related questionnaires. This will indicate the most suitable assessment(s) required to uncover sleep related disorders in OI, hopefully developing a screening tool for future use and reducing the need for full PSG inpatient assessments.
Reference
1. Moldosky H. Sleep and pain. Sleep Medicine Reviews. 2001;5:387–398
Disclosure
The authors declared no competing interests.
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P197

A playful type of intervention for infants with osteogenesis imperfecta

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Background
'Play Plans' are now being routinely used at the NHS England Sheffield Severe, Complex and Atypical Osteogenesis Imperfecta Service (SCAOI) as an intervention designed to enhance early development. These plans are MDT formulated and encompass carefully targeted activities designed to meet the child's needs at their exact stages of development across five domains; Cognition, Social & Emotional Development, Motor, Adaptive Skills and Communication & Language. Presenting Problem. Infants with SCAOI often have delayed motor development due to a number of factors including physiology, fractures and positioning for protection of the spine. Historically OT/Physiotherapy focus was on motor development however now as an MDT we are integrating Bayley's assessment with purposeful play to meet the global needs of infants including focus on cognition and attachment as well as motor skills. Evidence is limited regarding interventions to enhance early development in OI and as such a service evaluation is being undertaken at Sheffield Children's Hospital to assess the effectiveness of targeted 'Play Plans'. These plans carefully track the Bayley's assessment domains and are aimed to enhance development by targeting next stage developmental gains.
Clinical management
This presentation details the service evaluation outcomes in terms of development of plans and perceived benefit by parents and professionals. Examples of plans developed from Bayley's assessments are presented to demonstrate types of activity prescribed in conjunction with the desired developmental objective. One such example is targeting the lack of 'object permanence' (cognitive skill) in a 12 month-old by the recommendation of activities involving hiding and presenting of objects, toys and faces whilst also incorporating motor development by recommending positioning for this activity. The plans also include examples of toys specifically selected to be suitable for the motor ability of infants with OI whilst also being developmentally appropriate. These toys help advance learning rather than just being physically suitable. Parents have reported that knowing which toys to use and how to play with their child can be hard and as such have valued the guidance given in the plans.
Discussion
Play plans are perceived to be useful by families and clinicians in enhancing targeted developmental play.
Disclosure
The authors declared no competing interests.

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P198

The multidisciplinary team (MDT) approach: What does it look like and why does it matter? An illustration of a true MDT approach to provide holistic care for a child with severe and complex osteogenesis imperfecta

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Background
Addressing the needs of a child with Severe, Complex or Atypical Osteogenesis Imperfecta (SCAOI) requires a full MDT approach to enable the child to access their environment and meet their true potential. MDT input is essential in ensuring the delivery of medicine, participation in meaningful activity and supporting of the functioning of the child and family in complex systems.
Presenting problem
Osteogenesis Imperfecta (OI) impacts upon all areas of life and as such timely holistic assessment and intervention enables children to realise their potential. We illustrate this using a case example of a child with Type III OI supported by an MDT systemic intervention.
Clinical management
We illustrate in this presentation the benefits of a 'systems approach' to assessment, case conceptualisation, intervention and evaluation. Tarrier & Calam (2002) demonstrated the importance of a systemic approach to holistic case conceptualisation in the need to integrate social, psychological and epidemiological factors to understand a problem a person is experiencing. Clinically we recommend the need for MDT approach not only for invention but in the complex formulation of treatment pathways ensuring the child and family receive timely and appropriate care. This case example looks at a problem arising for a child with SCAOI at the age of 6 when the the family presented the team with the following question 'Is the special school our child is in going to meeting her needs?' This complex question was simplified using a systems approach by further assessments including Weschler Scales of Intelligence, Physiotherapy & Occupational Therapy assessment, equipment provision and testing as well as family reflective space enabling a collaborative case conceptualisation to be formed with the family. The family were empowered by the process to make the decision and transition the child into mainstream education where she was supported by the findings of the Weschler Scales (normal intelligence) and the provision of equipment such as the Madita Mini Chair to enable full classroom participation.
Discussion
Evidence based MDT intervention enables complex problem resolution for children and adults with OI, contributing towards the realisation of their true potential.
Disclosure
The authors declared no competing interests.

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P199

Diversity of outcomes in randomised trials of interventions for children with osteogenesis imperfecta

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Objective
The potential for clinical trials to impact patient care may be limited if the outcomes reported vary by trial and lack direct relevance to patients. We aimed to systematically assess the scope and consistency of outcomes reported in randomised trials of interventions for children with osteogenesis imperfecta.
Methods
We systematically searched for all published and unpublished randomised trials of interventions for children with osteogenesis imperfecta. Trials including adults were excluded but there were no other exclusion criteria. We extracted and analysed the frequency and characteristics of the outcome domains and measures.
Results
From 21 publications of 19 trials with 857 children included, 1782 different measurements of 60 different outcome domains were reported. There was a median of 14 outcome domains reported per trial (interquartile range 12 to 17). Overall, 33 domains (55%) were surrogate e.g. serum calcium, 23 (38%) were clinical e.g. vertebral fracture, and 4 (7%) were patient reported e.g. pain. From all outcome measures assessed, bone density (288 or 16%, 16 trials) and bone turnover markers (122 or 7%, 14 trials) were the two most commonly reported, while pain (32 or 2%, 6 trials) and fatigue (4 or <1%, 1 trial) were infrequently reported.
Conclusion
The outcomes reported in clinical trials involving children with osteogenesis imperfecta are extremely heterogeneous and are often focused on surrogate outcomes, rather than clinical and patient-focussed outcomes. There is also extreme diversity and heterogeneity at every level: domain, measure, and time point. A limitation of this study is that the data extracted was limited by the quality of the available reports, but this also reflects the real-life experience of end users of the medical literature. Efforts to ensure consistent reporting of outcomes and international patient registries with pre-defined outcomes that are important to patients and clinicians will improve the value of trials in guiding clinical decision-making.
Disclosure
The authors declared no competing interests.

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P200

Whole body vibration training for children and adolescents with congenital myopathy

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Objectives
To evaluate the effect of 24 weeks of weight bearing vibration therapy (WBVT) on muscle strength, motor function and bone health in children with congenital myopathies.
Methods
A prospective pilot study incorporating a six month observational period followed by 6 months home-based WBVT (Galileo® Pro) was undertaken. Ambulant children with congenital myopathies aged 4–16 years were eligible for inclusion. Participants were assessed at baseline, immediately prior to starting WBVT and following completion of WBVT. Lower limb muscle strength was assessed with hand held dynamometry. The Motor Function Measure and the six minute walk test assessed motor function, and bone health was assessed with dual energy xray absorptiometry (DXA). Paired t-tests were used to compare the change in outcomes between the observational and treatment period.
Results
Nine children (6 male, mean age 8.3 years) participated in the study, with 8 children completing all assessments. There was a significant difference in the change in total lower limb muscle strength between the observation and treatment period (mean difference 27.5N, 95% CI 1.2 to 53.8, $P=0.04$). There were no statistically significant differences between the change within the observation and treatment periods measured by the Motor Function Measure (mean difference 2/96, 95% CI −6.4 to 10.4, $P=0.58$) or the six minute walk test (mean difference 37.3 m, 95% CI −10.4 to 85, $P=0.1$). There were also no significant differences in height and gender matched z-scores for Total Body Bone Mineral Content (mean difference −0.06, 95% CI −0.06 to 0.19, $P=0.28$) or Total Body Bone Mineral Density (mean difference=0.00, 95% CI −0.22 to 0.22, $P=1.0$). No adverse events were reported.
Conclusion
WBVT was safe and well tolerated in children with congenital myopathies. A statistically significant improvement in lower limb strength, and a clinically significant improvement in the six minute walk test distance, was demonstrated following vibration training in comparison to the observation only period.
Disclosure
The authors declared no competing interests.

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P201

Juvenile dermatomyositis (JDM) and hypoparathyroidism (HP) in an adolescent girl

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Background
JDM is a systemic autoimmune inflammatory myopathy consisting of symmetric proximal muscle weakness, heliotrope and/or malar rash, Gottron's papules, nailfold capillary changes, myalgias, arthralgias, dysphonia, dysphagia, fever, anorexia, and calcinosis. Hypoparathyroidism can present with signs of hypocalcemia (numbness, tingling, bronchospasm, seizure, or tetany). Causes of HP include postoperative, autoimmune (isolated or in autoimmune polyglandular syndromes (APS) (AIRE gene in APS1)) or syndromic (i.e. DiGeorge syndrome). Autoimmune HP has been associated with many antibodies; both NALP5 and Ca sensing receptor antibodies may functionally impair PTH release (instead of causing gland destruction). Myopathy without weakness has been reported as a presenting feature of HP. Both disorders have been seen with other autoimmune disease (AD) in the same person, but have not been described together.
Presenting problem
A 15 year old girl presented with progressive leg and arm weakness and leg and trunk rash. Muscle biopsy confirmed dermatomyositis and laboratory evaluation revealed elevated inflammatory markers and hypocalcemia (6.7 mg/dl).
Clinical management
She was managed with IV methylprednisolone (MP) and methotrexate for JDM. Ca ranged from 7.2–8.5 mg/dl until MP frequency decreased, when Ca dropped to 6.1 mg/dl and she was started on oral calcium and ergocalciferol. Hypocalcemia persisted (6 mg/dl, iCa 0.81 mM) and was associated with hyperphosphatemia (6.7 mg/dl), and HP (PTH 5 pg/ml). She required IV Ca and has been managed with oral Ca, calcitriol, and sevelamer. We suspect autoimmune HP; AIRE gene studies were normal. JDM and HP have had a waxing and waning course. Much disease activity has been unpredictable; however, she has developed hypercalcemia and variable Ca, calcitriol and sevelamer needs which appear to correlate inversely with the degree of immune suppression needed for JDM.
Discussion
JDM and HP are autoimmune diseases which each carry significant morbidity and affect overall and health-related quality of life (QOL). To our knowledge, this is the first reported case of JDM and HP coexisting in a single patient. In this patient, the complex effects on QOL seem to be exacerbated by possible interaction of the diseases themselves and/or changes in one disease due to treatment of the other.
Disclosure
The authors declared no competing interests.

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P202

Vibration therapy improves mobility and has no detrimental impact on bone health in adolescents with mild cerebral palsy independent of daily protocol duration (9 minutes/day vs. 15 minutes/day)

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Adolescents with cerebral palsy (CP) have altered muscle tone and reduced bone mass, which can lead to impaired mobility and function increasing their risk for osteopenia in later life. OBJECTIVES: We evaluated the efficacy of two side-alternating vibration therapy (VT) protocols (9 minutes/day versus 15 - minutes/day) over a 20-week program on mobility and bone health in adolescents with mild CP. METHODS: Sixteen participants (12.4±0.9 years; 10 males) with mild cerebral palsy were recruited for the 15 minutes/day VT protocol. Retrospective data from 33 participants (15.9±0.5 years; 22 males) that performed the 9 minutes/day VT protocol were used as comparison. Assessments included the 6-minute walk test and whole-body dual-energy X-ray absorptiometry at baseline and after 20 weeks of intervention. RESULTS: Twenty weeks of VT increased the distance walked in the six-minute walk test by 11% in the 9 minutes/day group (+45 m; $P<0.001$) and by 9% in the 15 minutes/day group (+40 m; $P=0.003$). Comparison between the adjusted change in mobility of the two training protocols showed no differences ($P=0.77$). Lean mass increased in both the 9 minutes/day group ($P=0.001$) and 15 minutes/day group ($P=0.05$) but percentage lean mass remained the same and there was no difference between protocols ($P=0.11$). Participants in the 9 minutes/day group increased total body bone mineral content and density ($P<0.001$ & $P=0.005$, respectively) while the participants in the 15 minutes/day group increased total body bone mineral content ($P=0.005$) after intervention. Both groups increased spine bone mineral density ($P=0.005$ & $P=0.005$ respectively). Adjusted changes in bone composition were only significantly different between protocols for spine bone mineral density, which showed a greater change with the 15 minutes/day group ($P=0.036$). CONCLUSION: VT was an effective intervention in increasing mobility with no detrimental impact on body composition and bone heath in adolescents with mild CP. However extending the duration of training had no effect on 20 week outcomes.
Disclosure
The authors declared no competing interests.

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P203

Side-alternating vibration training improves mobility and has no detrimental impact on bone health in young children with mild-moderate cerebral palsy

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Children with cerebral palsy have altered muscle tone and reduced bone mass, which can lead to impaired mobility and function increasing their risk for osteopenia in later life.
Objectives
We aimed to evaluate the impact of 20 weeks of side-alternating vibration therapy on muscle and bone health in children with mild-moderate cerebral palsy. METHODS: Twelve participants (7.2±0.5 years; 6 females) were recruited to perform vibration therapy on a Galileo platform 9 minutes/day, 4 times/week at

20 Hz. Assessments included the six-minute walk test and whole-body and spine dual-energy X-ray absorptiometry at baseline and after 20 weeks of intervention.
Results
Twenty weeks of vibration therapy increased the distance participants walked in the six-minute walk test by 13% (362 vs 410 m; $P<0.001$) with sustained reductions in the time taken to reach individual milestones. Over this time participants increased in height (+1.9 cm; $P<0.001$) and total body mass (+1.88 kg; $P<0.001$) with associated changes in fat mass (+0.83 g; $P=0.013$) and lean mass (+0.42 g; $P<0.001$). Importantly, bone mineral content increased in the total body (+63 g $P=0.002$), leg (+24 g; $P<0.001$), trunk (+23 g; $P=0.034$), pelvis (+10 g; $P=0.011$) and L1–L4 spine (+1.15 g; $P=0.001$). Bone mineral density also increased in the total body (+0.013 g/cm^2; $P=0.003$), leg (+0.027 g/cm^2; $P=0.005$), trunk (+0.014 g/cm^2; $P=0.014$), pelvis (+0.024 g/cm^2; $P<0.001$) and L1–L4 spine (+0.020 g/cm^2; $P=0.011$) measures.
Conclusion
Twenty weeks of vibration therapy in mid childhood was associated with increased mobility. Overall growth, muscle mass, fat mass and bone density improved and there was no evidence of any deleterious effect of vibration therapy.
Disclosure
The authors declared no competing interests.
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P204

A qualitative analysis of the burden-of-illness associated with X-linked hypophosphataemia (XLH) in children and adolescents
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Objectives
XLH is a rare, genetic, inherited disorder characterised by low blood phosphate which leads to inadequate mineralisation of bone, resulting in a spectrum of skeletal and functional muscle abnormalities, abnormal tooth development, physical and functional impairments. Treatment with conventional therapy places a significant burden on patients and families; it can require complex treatment dosage schedules, is often poorly tolerated, and can be associated with serious complications. The aim of this study was to qualitatively analyse the burden of XLH in children and adolescents as reported in patient and caregiver testimonies.
Methods
During an appraisal of a new treatment for XLH conducted by the National Institute for Health and Care Excellence (NICE), a public consultation was undertaken in which 93 testimonies were provided by patients, their families, healthcare providers and other stakeholders on the burden of the condition. Hybrid deductive and inductive thematic analysis was used to analyse 41 testimonies related to children or adolescents with XLH. Two reviewers independently coded and analysed the responses according to 12 themes, with differences settled through third party consensus.
Results
The majority of consultation responses were from parents of affected individuals. The experiences revealed symptoms associated with XLH, including bone deformities and short stature, were frequently related to general pain and mental well-being (stress). Short stature was often expressed alongside experiences of bullying and low self-esteem. Conventional treatment in childhood, typically a complex multi-daily dose regimen of oral phosphate and Vitamin D, was a common complaint for patients and placed strains on their families. Dosing regimen, non-adherence, taste and adverse effects were most likely to be related to treatment burden with conventional therapy. The treatment burden theme was highly associated with families with multiple children with the strain of medication administration.
Conclusion
Our findings indicate the burden of illness in XLH in this age group is multi-factorial. Symptoms related to skeletal complaints suggest certain themes are organically-driven by functional impairments, while complaints in the burden of treatment also have a notable psychological and wider family impact. Qualitative analysis of XLH can inform the understanding of the burden of disease from the patient perspective.
Disclosure
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P205

Bone mineral density in surgical hemivertebrae treatment in a prematurely born child − a case study
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Introduction
Presence of osteosynthetic material in the spinal region may result in decreased musculoskeletal activity in certain spinal column segments, leading to vertebral bone mineral density changes.
Case study
The case involves a 12-year-old girl who was born prematurely, who complained of experiencing lower back pain after performing forward roll in the physical education class. The patient was born at 32 weeks of gestation by pelvic presentation, weighing 1350 g, and measuring 37 cm, with the Apgar Score of 2/4/6. She subsequently experienced motor and cognitive developmental delays. CT and MRI findings confirmed hemivertebrae in L1, scoliosis, narrowing of intervertebral spaces VTh11−VL2, disc protrusion at the VL5−S1 level with intense impression on the nerve root in the right neural foramen region. Egg Shell surgery was performed, involving instrumentation placement and compression-distraction positioning, after which the patient underwent postoperative rehabilitation therapy. Regular follow-ups and physical therapy were provided, in line with the recommendations for the surgery type performed. Bone mineral density in the lower lumbar vertebrae L2−L4 was assessed via DXA three years following the surgery, whereby Z score of 0.5 was obtained for both hip and spine, which is within normal limits. Owing to Vitamin D deficiency, supplements were prescribed. The patient remains free of any subjective symptoms, her gait schema has been corrected, and her endurance while standing as well as in all everyday activities has been improved.
Conclusion
Patients with osteosynthetic material in the spinal column require multi-disciplinary follow-up, including bone metabolism parameter monitoring.
Keywords
bone mineral density, hemivertebrae, children
Disclosure
The authors declared no competing interests.
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P206

Robot-assisted exercises in children with cerebral palsy – a case study
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Introduction
Rehabilitation therapy in children with cerebral palsy is a continuous process spanning several years and necessitating good cooperation between the child and all team members.
Case study
The case involves 11-year-old girl, diagnosed with cerebral palsy GMFCS Level II of diplegic form. She can walk with support, but her stability and balance is compromised. Instability in seated position is also present. The patient underwent rehabilitation therapy involving a physiotherapist and robot MARKO in hospital setting. Daily 30-minute sessions took place in the kinesitherapy room. Under the supervision of her doctor and physiotherapist, the patient performed previously learned exercises when prompted by the humanoid robot. During the session, the humanoid robot asked the patient specific questions, thus obtaining information about her current condition and degree of tiredness. Upon completion of the 10-session treatment, the child developed greater motivation and resilience when performing the planned set of exercises. The patient indicated preference for exercising with the robot and is keen to continue therapy.
Conclusion
Patient's motivation to engage in physical therapy may vary with time and can be improved by incorporating modern technology in the exercise program.

Keywords
robot-assisted therapy, cerebral palsy, children
Disclosure
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P207

Group exercises aimed at poor body posture correction assisted by humanoid robot – A case study

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Introduction
Insufficient physical activity may lead to poor body posture, especially during periods of rapid growth and development. As teenagers tend to find exercising boring and are unlikely to perform prescribed exercises at home, parental oversight and guidance is required.
Case study
The reported case pertains to the program of corrective symmetric exercises conducted at the Institute of Child and Youth Health Care of Vojvodina, Novi Sad, involving a group of five children of both genders aged 8−16 years, all of whom presented with poor body posture. Five treatments were performed in the first week, whereby patients engaged in exercises in the kinesitherapy room under the supervision of physiotherapist. In the second week, the same five treatments were conducted, but the children were assisted by a humanoid robot MARKO (in Serbian, MARKO is the acronym of Mobile Anthropomorphic Robot with Cognitive Characteristics). Each session lasted 30 minutes. Upon treatment completion, children were asked if they found exercising with the robot easier, whether the robot motivated them to persevere during the session and if they would be willing to continue exercising. All children rated robot-assisted exercises positively.
Conclusion
Involving a humanoid robot in a corrective exercise program can improve child engagement, as the exercises become more interesting and are thus better accepted by teenagers.
Keywords
exercise, children, humanoid robot
Disclosure
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P208

Motor developmental outcomes in 2 babies with very severe osteogenesis imperfecta (type II)

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Introduction
Although previously babies with genetic type II Osteogenesis Imperfecta (OI) would not have expected to survive, they are now surviving beyond the neonatal period. We describe two such children who have survived beyond infancy.
Aim & methods
To identify differences in motor developmental progress between a typical severe (type III) OI child vs two Type II OI children and suggest possible causes. Medical, nursing and therapy (physiotherapy and occupational therapy) notes were reviewed and compared for the 3 patients. Significant medical events (respiratory, neurosurgical interventions and fractures) and developmental milestones were identified. Contact time with Multi-Disciplinary Team [MDT] (excluding doctors) was recorded from the hospital activity system.
Results
Motor outcomes were grossly delayed in the Type II vs Type III baby despite intense input from physiotherapy, mean hours (73.75 vs 30.25) in the first 10 months of life. Children (A & B) with type II OI achieved active head turns in supine at age 9 and 4 months respectively vs age 3 months in child C (type III). Independent rolling -supine to prone- was achieved age 18 months in child A, not yet achieved in child B but achieved by age 14 months in child C. Ability to lift head in prone was achieved age 3 months in child C but at age 18 months in child A and not yet achieved in child B (now age 19 months). Number of fractures in all 3 babies in the first year of life was low A = 2, B = 1 vs C = 2. Significant medical events affecting respiratory, feeding and neurological function were more frequent in the Type II babies. Similarly, inpatient time in the first year of life was greater in the Type II vs Type III OI (mean 312.5 vs 62 days).
Conclusion
Babies with type II OI are likely to have complex medical problems which affect their motor development. Although bone fragility precautions are important, other factors seem to have a greater impact. They are also very likely to require much higher long term therapy input which should be factored into care planning.
Disclosure
The authors declared no competing interests.
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P209

Persistently low trabecular bone mineral density and normal bone strength at the radius over 3 years after simultaneous pancreas kidney transplantation

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Objectives
Simultaneous pancreas kidney transplantation (SPKT) is a standard treatment option for adults with long-lasting (usually adolescence onset) type 1 diabetes (T1D) and concurrent renal failure. Despite the need for life-long immunosuppressive therapy the patients achieve better glycemic control, normalized renal function and an improved quality of life. Whether metabolic improvement is also reflected in the skeleton is not yet clear.
Methods
Patients were prospectively followed after SPKT performed at a single tertiary center between November 2011 and December 2014. Besides routine blood tests, the subjects were scanned by DXA at the spine and femur and by pQCT at the forearm within 3 months and then 1.3 and 3.3 years after the transplantation. One sample t-test was used to analyze the difference of the *Z*-scores of the bone parameters from zero and study end was compared to baseline by the two sample t-test.
Results
There were 32 patients (9 females) with T1D aged 44.2 ± 9.6 years (mean ± S.D.) at the time of transplantation, mean age at T1D manifestation was 17.7 ± 9.6 years. The lumbar spine (LS) bone mineral density (BMD) was decreased at the baseline (*Z*-score −1.2 ± 1.3, $P < 0.001$), 8/32 (25%) patients had BMD *Z*-score ≤ −2.0. The mean LS BMD *Z*-score normalized at the study end (*Z*-score −0.2 ± 1.2, $P = 0.39$). The femoral neck (FN) BMD was low at the baseline (*Z*-score −1.5 ± 0.9, $P < 0.001$), 10/32 (31%) patients had BMD *Z*-score ≤ −2.0. The FN BMD *Z*-score was still low at the study end (*Z*-score −1.2 ± 0.9, $P < 0.001$) and did not change significantly 3 years post transplantation ($P = 0.31$). In contrast to LS BMD, trabecular volumetric BMD (vBMD) at the metaphysis of the radius was low at both time points (*Z*-scores −1.3 ± 1.2, resp. −1.3 ± 1.0; $P < 0.001$ for both). Cortical vBMD assessed at the diaphysis of the radius was normal at baseline and also at study end (*Z*-scores 0.0 ± 1.3, $P = 0.98$; and −0.45 ± 1.5, $P = 0.09$, respectively). Similar findings were observed for the Strength-Strain Index.
Conclusion
This is the first study examining the development of volumetric, size independent, BMD in patients after SPKT. How do the discordant areal and volumetric BMD findings relate to fracture risk in these patients remains to be elucidated.
Disclosure
The authors declared no competing interests.
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P210

Premature physeal closure following 13 -cis - retinoic acid administration in neuroblastoma

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Background
Isotretinoin has demonstrated efficacy in a wide range of disorders. The beneficial effects of the drug, however, are limited by its adverse impact on the bone. Children exposed to high doses are at risk for premature epiphyseal closure, while adults on long-term therapy have an increased tendency to develop hyperostosis and other changes of the bone. Presenting feature and Clinical management A 9-month-old infant presented with vomiting and distended abdomen due to hepatomegaly. CT scan confirmed a left adrenal tumor with multiple liver metastatic lesions and right adrenal mass.Urine VMA/Creatinine was 63.8 umol/mmol (normal $<$ 4.7) and LDH 2333 U/l (normal: 163–452). Ultrasound guided biopsy of liver lesions confirmed a diagnosis of poorly differentiated neuroblastoma. Patient was treated as for high risk neuroblastoma with chemotherapy followed by surgery (bilateral partial adrenalectomy and liver segmentectomies). MRI showed residual liver lesions which was treated with radiation and cis-retinoic acid for 6 months. After 31/2 years patient developed swelling of bilateral lateral malleoli. X-ray of the lower limb showed bilateral widening & cupping of distal tibial metaphysis with reduced bone density and relative shortening of both tibias as compared to fibulas. Bone MRI showed premature fusion with bony bridging affecting central aspect of the growth plate at both distal tibias, affecting 10–15% (left) and 20% (right) of the cross-sectional area of the growth plate. Distal fibular growth plate was open.Patient underwent surgical removal of physeal bar with fat interpositioning between the growth plate and metaphysis and is under monitoring for 'DISH' like diffuse skeletal hyperostosis.
Discussion
The effects of retinoids on bone may be profound and include progressive calcification of ligaments and tendon insertions, premature fusion of epiphyses, modelling abnormalities of long bones, and perhaps osteoporosis. Although it has been known since 1933 that vitamin A cause bone abnormalities, the mechanism of this effect has been elusive. Recent work suggests a possible relationship of the retinoids with several cytokines, which results in enhanced maturation of the preosteoclast. The knowledge of these effects, in conjunction with continued surveillance, are necessary for expert management and can ensure many years of efficient treatment with minimal toxicity.
Disclosure
The authors declared no competing interests.

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P211

Value of osteogenesis imperfecta clinical nurse specialists to families and consultants across five UK centres

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Objectives
To ascertain if parents and consultants at secondary care level hospitals felt there were areas that the Clinical Nurse Specialists (CNS), working with children and families with Osteogenesis Imperfecta (OI) could improve upon within their service, and to gain feedback on the current service provided.
Methods
A SurveyMonkey© questionnaire was created through the audit team at Great Ormond Street Hospital and the Paediatric Osteogenesis Imperfecta National Team (POINT) nursing break-out forum. These data were then compiled and collated into graphs and visual displays. Areas for improvement were fed back to individual services to consider how they may improve as a service, and as a collective group in POINT.
Results
In total 46 parents and 25 consultants completed questionnaires from 5 UK Hospitals, including the 4 designated Highly Specialised OI services in England. 89% of parents reported a CNS being present in their last OI appointment. 100% reported knowing how to contact the CNS. 83% agreed that 'The OI CNS role supports me to manage my child's OI'. Areas to improve included: having more than 1 CNS, giving more information to schools and spending more time with the nurse at hospital appointments. Additional comments included: 'My CNS plays an important role in my daughter's life'; 'Couldn't be without our CNS'; 'Reassuring to have available'; 'Goes above and beyond in the role'. 88% of external Consultants reported they were aware of a CNS in their regional OI centre. Reasons for contact included: blood results, referral information, prenatal planning and medication queries. The benefits listed included: single point of contact, expert advice. 77% reported they agreed that 'The OI CNS is a good point of contact to assist me to manage my patients with Osteogenesis Imperfecta'. These data were exclusively linked to one centre reflecting a more hub and spoke model of care, partly necessitated by the geographical location of patients (London and the South East).
Conclusion
Results showed that parents and external consultants value the role of the CNS both as a point of contact and as a source of specialist OI advice and support.
Disclosure
The authors declared no competing interests.

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P212

Genetic loss of heparanase does not inhibit osteochondromas in Ext1 and Ext2 double heterozygous hereditary multiple osteochondroma mouse model

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Hereditary multiple osteochondromas (HMO) is an autosomal dominant rare genetic disorder due to LOF heterozygous mutations in EXT1 or EXT2 genes. HMO is an unmet medical condition where patients often requiring multiple surgeries. HMO is characterized by painful cartilaginous capped bony outgrowths at the growth plate (GP) regions of long bones, ribs and other skeletal elements. The molecular mechanism by which these mutations lead to disease is unknown. Mutations in EXT1 and 2 cause impaired heparan sulfate (HS) chain elongation, resulting in short chain HS and abnormal cartilage matrix in bone, which may affect various growth factors that are modulated by HS binding. Previous studies have shown that human HMO lesions express heparanase in chondrocytes of all layers of the GP in contrast to normal GP, where it is restricted to hypertrophic chondrocytes. Heparanase upregulation is thought to induce HS cleavage and promote ectopic BMP signaling, resulting in osteochondromas development. We tested the hypothesis that heparanase inhibition would abrogate osteochondroma development in double heterozygous Ext1 and Ext2 mice. We developed a mouse model of HMO by crossing Ext1 with Ext2 heterozygous mice. Ext1+/−, Ext2+/− and double heterozygous were born alive without any gross abnormalities and overall skeletal development was indistinguishable from control litter mates. Single and double heterozygous mice developed osteochondromas in the ribs, however double heterozygous mice have higher incidence (Ext1+/− 50%, Ext2+/− 38% and Ext1+/− and Ext2+/− 67% of mice developed osteochondromas at 20 weeks of age). Development of osteochondromas is also increased over time in double heterozygous mice, 41% of 8 week old mice developed osteochondromas, increasing to 83% at 24–28 weeks. To determine role of heparanase in the development of osteochondromas, we generated heparanase knockout mice and crossed with Ext1 and Ext2 double heterozygous mice to delete heparanase in the HMO mouse model. We observed that genetic loss of heparanase did not inhibit development of rib osteochondromas, 88% of heparanase KO HMO mice and 92% of HMO mice developed osteochondromas at 33–34 weeks of age. Our mice genetics study revealed that loss of heparanase did not affect osteochondromas development.
Disclosure
All the authors are employed by Regeneron Pharmaceuticals Inc and owners of company stock.

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P213

Evaluating a therapy-led school and nursery outreach service for children with Osteogenesis Imperfecta

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Objective
Osteogenesis Imperfecta (OI) is most commonly caused by a defect in the genes which produce type 1 collagen. Features of OI include easy fracturing, short stature, hypermobility, weakness and fatigue. Our experience is that including a child with OI within a school or nursery environment can cause anxiety for both carers and staff. Questions often arise regarding how to promote participation whilst maintaining a child's safety. Keeping up with the curriculum can be challenging for some children. The Physiotherapy and Occupational Therapy team at a specialist paediatric OI centre offer a school and nursery outreach service. Topics frequently addressed include appropriate inclusion in physical education, risk and environmental assessments, recommending suitable equipment and strategies, as well as providing education to staff about OI. The outreach service was evaluated to investigate its effectiveness and identify areas of improvement.
Method
A questionnaire was sent out to schools and nurseries which had been visited by the OI therapy team. Questionnaires were sent out electronically and responses anonymised.
Results
To date 11 questionnaires have been sent and 9 returned, some of which were incomplete. 100% of those who responded reported information on safety considerations and environmental and risk assessments to have been most beneficial. 50% reported equipment advice and information on OI was beneficial. 25% found information on participation and fracture management beneficial. 75% of respondents felt another outreach visit would be helpful. Following the visit, all reported an increase in confidence in their understanding of OI. Furthermore all reported an increase in their ability to modify the environment appropriately to ensure participation.
Conclusions
Based on these results, those surveyed found the outreach service valuable, citing the information on OI, modifying the environment/activity and managing risk as being the most beneficial. We have been able to identify areas of need and also areas of development such as follow up visits. Our evaluation is on-going with the aim of collating more robust data to evidence the provision. We will use these results to offer schools and nurseries the support they require and modify our existing service accordingly.
Disclosure
The authors declared no competing interests.

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P214

Assessment of multidisciplinary care of children with osteogenesis imperfecta at The Royal Manchester Children's Hospital

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Dedicated occupational therapy and physiotherapy service for children and families with Osteogenesis Imperfecta (OI) at the Royal Manchester Children's Hospital were set up in September 2017 to provide multidisciplinary management.
Objectives
The aim is to assess if the newly established specialist paediatric occupational therapy and physiotherapy service is meeting the needs of the patients and their families.
Method
A paper questionnaire with an electronic link was distributed to families during their hospital attendance. The questionnaire comprising 10 questions looked at gaining information regarding: - Usefulness of assessment and advice provided during individual sessions and during multi-disciplinary OI clinics
- Satisfaction with the service provided
- Helpfulness of home visits, school visits and written reports
- Therapy services which may be beneficial to offer in the future
Results
The questionnaire has been distributed to 25 families. The response rate for the questionnaire is 65%. Of the respondents 73% were parents. All respondents gave highest rank to the advice and information provided to them for management of OI. 73% of the respondents had attended a multidisciplinary clinic and 66% had rated their satisfaction level of the experience at 8 or above, 10 being the most satisfied. 66% rated the written reports received following clinic as excellent or good. 60% had been seen whilst attending hospital for infusions and 53% rated the experience as useful. School visits and home visits had been carried out with 33% of respondents and these had been rated as definitely helpful. 80% of the respondents rated their overall satisfaction with the service as 8 or above, 10 being most satisfied. With regards to future developments, patients/families suggested group sessions to share their experiences, written information tailored specifically to the needs of their child and local OI family days.
Conclusion
The patient/families current opinion of the specialist therapy was positive. We are using the valuable feedback to enhance our services paying special attention to providing individualized written information regarding OI. We are also planning to organise family days for patients/families.
Disclosure
The authors declared no competing interests.

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P215

Evaluating the natural history of subcutaneous fat necrosis

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Background
Subcutaneous fat necrosis (SCFN) of the newborn is an uncommon condition most commonly seen in term infants who have experienced perinatal stress presenting as nodules or plaques on the face, back or upper extremities. The associated complication of hypercalcemia is thought to be secondary to elevated 1,25-OH vitamin D from increased expression of 1-alpha hydroxylase from inflammatory granulomatous cells. However the natural history of SCFN, associated hypercalcemia and its possible long term effects has not been well described. Clinical observation at the Hospital for Sick Children (HSC) suggests that ongoing hypercalcemia, albeit less severe than at presentation, persists for a number of months beyond the resolution of palpable nodules. Given this, our objectives were to evaluate the natural history of SCFN, associated hypercalcemia and serial laboratory values.
Cases
We reviewed the cases of 8 children diagnosed with SCFN and associated hypercalcemia followed in the HSC Calcium Clinic; 7 of 8 followed to resolution. Of the 8 children; 5 presented following hypoxic ischemic encephalopathy and cooling, 1 following traumatic vacuum assisted delivery and 2 were found to have incidental skin lesions. On average hypercalcemia was detected at 1 month of age, with a peak calcium value of 3.42 ± 0.56 mmol/L. The children were typically seen in follow up every 4 months, and after initial hospital treatment, were managed on a restricted calcium intake. Based on serial clinical exams, palpable subcutaneous nodules resolved on average after 10.5 ± 7.6 months. The resolution of hypercalcemia lagged behind, with a normalization of serum calcium occurring at 25.3 ± 9.5 months. Four of the children developed nephrocalcinosis These children had the highest peak serum calcium values at diagnosis of the group.
Discussion
Given hypercalcemia can persist well beyond the clinical resolution of nodules, there is risk that these children may be discharged from follow-up prematurely with possible persistent urinary calcium excretion and risk of nephrocalcinosis. A closer look at other, possibly predictive factors, including 1,25 vitamin D levels and duration of dietary restriction may be useful in guiding our future monitoring and management of these patients.
Disclosure
The authors declared no competing interests.

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P216

Dual diagnosis of autism and osteogenesis imperfecta: Case examples to illustrate the implications of dual diagnosis for enhanced outcomes for child and family

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Background
A minority of children with Osteogenesis Imperfecta (OI) seen within the Sheffield National Severe, Complex and Atypical Service (SCAOI) were also identified as showing symptoms consistent with an Autism Spectrum Disorder (ASD) (Balasubramanian *et al*. 2018). Diagnosis of ASD in conjunction with OI may be delayed due to presenting problems being inappropriately attributed to OI resulting in specialised ASD input not being received by children.
Presenting problem
We present two case examples of young children seen within the NHS England Severe and Complex Osteogenesis Imperfecta Service (SCAOI) who received additional diagnoses of ASD. These two children were aged 4 years and 6 years old at the time of diagnosis of ASD whereas they had received diagnoses of OI in infancy. Their early development was unusual, both displaying delayed language & communication. Apparent features that would be expected to be noticed in typical development included repetitive behaviours such as rocking/flapping and distinctly unusual communication styles and play. Neither child had been identified as potentially having ASD by community services such as health visitor checks or by nursery. Both children showed challenging behaviours.
Clinical management
Diagnosis of ASD has had significant positive effects for both children and their families. Professionals working with children with SCAOI need to be alert for ASD 'Red Flags'. This presentation details the diagnostic process, interventions and outcomes and includes Child A transitioning from mainstream to special school with the more supportive environment resulting in a significant decrease in problem behaviours. Child B remained in mainstream school but received specialist ASD support and the school benefited greatly from the understanding of the child in the context of their additional ASD diagnosis.
Discussion
Due to the possibility of dual diagnosis being overlooked as a result of the motor delay present with OI and a lack of understanding of OI outside of specialist services, it is very important for specialist services to notice ASD 'red flags' as detailed in this presentation and refer for full assessment where required.
Disclosure
NJB consults for Alexion, Mereo, UCB and Amgen, and receives grant support for clinical studies from Alexion and Amgen. PA receives Honoraria/expenses: Alexion and Kyowa Kirin and expenses from BioMarin.

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P217

Abstract withdrawn.

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P218

Hypercalcemia and parathyroid hormone-related peptide expression in a 3 months old boy with Colon Hemangioendothelioma

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Introduction
Epithelioid hemangioendothelioma (HEE) is a tumor of vascular origin, infrequent in the pediatric age and even more infrequent at intestinal level. To our knowledge, there are no previous reports of pediatric patients with malignant humoral hypercalcemia associated with this tumor. Humoral mechanism is seen more often in lung, uterine cérvix, skin and esophagus tumors. The presence of hypercalcemia appears to be an ominous prognostic sign.
Objective
To report the first case of a patient with hypercalcemia related to PTH-rP associated with Colon HEE in a pediatric patient.
Case description
A 3 months years old boy was admited because of clinical worsening and palpable abdominal mass. Initial laboratory investigation revealed hypercalcemia with the following workup: PTH: 1.65 pg/ml, calcium: 25.1 mg/dl, phosphorus 2.9 mg/dl 25ohvitamine D:25.2 ng/ml, Urine catecholamines were normal. Ultrasound visualized a highly vascularized tumor with calcifications in retroperitoneum of $8\times6\times6$ cm located between liver and right kidney. Biphosphonates and Calcitonin were iniciated without improvement. Biopsy reported epithelioid hemangioendothelioma and angiography revealed tumor irrigated by the middle colic artery. Selective embolization was performed with spongostan and 24 hours later, tumor exeresis was achieved. PTHrP mRNA was identified in the tumor. After surgery the patient attained normocalcemic state, PTH levels normalized and remained normocalcemic to date, 18 months later.
Conclusion
We report the first case of PTH-rp related hypercalcemia, with mesocolon epithelioid hemangioendothelioma a pediatric patient. PTH-rp mRNA was detected at tumor level, and the patient resolved hypercalcemia with tumor resection, remaining normocalcemic and with normal PTH levels since then. Selective embolization was important in order to facilitate tumor resection successfully, and improving morbidity and mortality of this surgery.
Disclosure
The authors declared no competing interests.

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P219

Comparison of cell separation methods, using relative expression of specific growth plate zone markers in a pig model

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Objective
Linear growth is achieved by enchondral ossification in epiphyseal growth plates (GP) of long bones. These highly organized cartilaginous tissues contain chondrocytes of all differentiational stages classified in 3–5 specific zones. Due to their discrete characteristics, distinct analysis of each zone is essential in basic GP research. While the efficiency of zonal separation is therefore highly influencing on study results, comparative data on commonly used methods are sparse. This study aims to compare the efficiency of density gradient centrifugation (DGC) and laser capture microdissection (LCM) by quantitative real time PCR (qRT-PCR) of zone-specific growth plate samples.
Methods
Primary chondrocytes and cartilage tissues were isolated from femoral and tibial growth plates of prepubertal piglets and separated by density gradient centrifugation and Laser Microdissection (LCM) respectively. Samples were evaluated by qRT-PCR for Secreted Frizzled Related Protein 5 (Sfrp5) and Collagen type X (ColX) expression as markers for resting and hypertrophic zone, respectively.
Results
Significant differences in marker gene expression for resting and hypertrophic zones as compared with their respective adjacent zones could be found in both separation methods. Both LCM and density gradient centrifugation were able to discriminate resting vs. proliferative zones by Sfrp5 expression values, although to different levels of significance (DGC: $P=0.034$; LCM $=0.003$). Comparable results were observed for ColX gene expression levels in hypertrophic versus proliferative zones (DGC $P=0.024$; LCM <0.001).
Conclusion
While both methods are able to discriminate growth plate zones, LCM achieved a higher level of significance in zonal separation as compared to DGC. Thus, LCM allows to minimize methodical bias and should be the preferred method for expressional studies on specific growth plate zones.
Disclosure
The authors declared no competing interests.

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P220

New perspectives in diagnosis and management of optic neuropathy in fibrous dysplasia: utility of optical coherence tomography and computed tomography measurements

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Objectives
Optic neuropathy (ON) is a critical complication of fibrous dysplasia (FD). Early surgical decompression can prevent blindness; however, prophylactic intervention may cause blindness from intra-operative nerve damage. There is therefore a critical need to develop diagnostic tests for accurate and early detection of ON in patients with FD. Currently used methodologies, including radiographic evaluation of optic canal size and optic nerve length, are suboptimal and correlate poorly with objective vision loss. Optical coherence tomography (OCT) has emerged as a potential tool due to its ability to detect retinal nerve fiber layer (RNFL) thinning, an early sign of optic nerve atrophy. The purpose of this study was to assess the diagnostic utility of OCT for evaluation of ON in patients with FD.
Methods
Subjects with craniofacial FD underwent neuro-ophthalmologic evaluation and OCT imaging ($N=70$, mean age = 23.5, range = 5–66). ON was diagnosed clinically, based on visual acuity, visual fields, color vision, contrast vision, and fundoscopic examination. The diagnostic utility of RNFL thickness was determined using ROC curve analysis, and accuracy was compared to radiographic optic canal measurements. Longitudinal changes in RNFL thickness were assessed.
Results
11 subjects had ON (8 unilateral/3 bilateral) for 14 total affected eyes. RNFL thickness accurately identified ON (AUC = 0.997, $P<0.0001$) with 100% sensitivity and 97% specificity when using a threshold of ≤ 71 μm. RNFL thickness outperformed radiographic measurements of optic canal area and optic nerve length ($P<0.05$). In subjects with normal vision, RNFL thickness decreased at an average rate of 0.21 μm/year ($P<0.01$). When analyzed longitudinally, RNFL increased during adolescence and declined after puberty.
Conclusions
OCT measurement of RNFL thickness is a superior test for identifying ON than radiographic optic canal narrowing or optic nerve elongation. Using a threshold RNFL thickness ≤ 71 μm, clinicians can identify ON in FD patients with high sensitivity and specificity. By establishing the normal rate of age-related RNFL changes, clinicians can monitor for abnormal RNFL loss over time and identify at-risk patients prior to irreversible damage. These findings have immediate clinical application that may help identify appropriate surgical candidates, reduce unnecessary interventions, and decrease the incidence of blindness in FD.
Disclosure
The authors declared no competing interests.

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P221

Speech and hearing impairment and respiratory complications in a large cohort of patients with Achondroplasia

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Objectives
Respiratory and Ear, Nose and Throat (ENT) complications are commonly reported in children with achondroplasia but little data is available regarding prevalence and outcome. In an unselected cohort of children with achondroplasia, we studied the prevalence of:

- Abnormal cardiorespiratory sleep studies
- Speech and hearing impairment
- ENT interventions
- Ventilatory support and respiratory outcomes

Methods
All children under 2 years undergo routine cardiorespiratory sleep study (CRSS) and retrospective data was collected on all patients over a 2 year period (Total $N=39$, mean age = 0.79 ± 0.41 years, Females $N=20$).
Data collected included: hearing impairment; speech delay; grommet insertion; the need for hearing aids; non invasive ventilatory support (such as continuous positive airway pressure (CPAP), insertion of nasopharyngeal airway (NPA) and oxygen requirement). CRSS and respiratory outcomes post ENT interventions were also collected.
Results
64% patients ($N=25$) had abnormal CRSS. 44% ($N=17$) had Obstructive Sleep Apnoea (OSA), 18% ($N=7$) mixed OSA and Central Apnoea, and 2% ($N=1$) Central Apnoea. 25% ($N=10$) had hearing impairment and 28% ($N=11$) speech delay. 38% ($N=15$) of patients had Tonsillectomy and or/Adenoidectomy interventions (T/A), 28% ($N=11$) had grommets inserted, 8%(N = 3) required hearing aids. 15% patients ($N=6$) required ventilatory support: 17% of these ($N=1$) had mild obstructive and central apnoea; 50% ($N=3$) had severe OSA and 33% ($N=2$) had mild OSA.
Respiratory support included: nocturnal CPAP ($N=4$, two also needed 24 h or nocturnal oxygen), NPA ($N=2$, one subsequently required CPAP). 83% ($N=5$) patients underwent either Tonsillectomy and/or Adenoidectomy (T/A). One patient was unable to undergo an ENT interventions due to age and remained on CPAP. Outcomes 1 year post T/A include; no respiratory support ($N=1$), nightly oxygen ($N=1$). NPA ($N=1$) and CPAP ($N=1$). One patient commenced CPAP aged 2.5 year despite 2 T&A operations.
Conclusion
Achondroplasia in young children is commonly associated with sleep apnoea (64%), hearing impairment (25%) and speech delay (28%). 38% of these children required T/A removal. Non invasive ventilatory support was needed in 15% which included nocturnal CPAP, NPA insertion and home oxygen. Despite T&A the majority of this subgroup still required ventilatory support after one year. Patients with Achondroplasia should be routinely screened for speech and language delay and respiratory complications.
Disclosure
The authors declared no competing interests.

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P222

Long-term clinical outcome in chronic recurrent multifocal osteomyelitis (CRMO): the Leiden cohort

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Objectives
To characterize clinical features and long-term outcome of CRMO, a rare inflammatory bone disease of childhood and adolescence, which forms part of the spectrum of chronic non-bacterial osteomyelitis (CNO).
Methods
We studied 33 patients with an established diagnosis of CRMO followed at the Centre for Bone Quality of the Leiden University Medical Center from 1994 to 2018. Demographic and clinical data were collected at presentation and last follow-up control.
Results
There were 22 girls and 11 boys with a median age of 11 years (range 5–17) at first symptom(s). Delay in diagnosis was 1.5 ± 2 years. Presentation was with acute bone pain in all, predominantly in one or more long bone. Local inflammatory manifestations (soft tissue and bone) were present in 14 patients and decreased function in 8. Five patients had palmoplantar pustulosis, and 11 an autoimmune disease, 6 psoriasis. Lesions of lower limbs were most common ($n=18$), mainly of tibia ($n=12$). Thirteen had sternocostoclavicular lesions, and one a mandibular lesion. The majority (73%) had multiple bone lesions (2–15). Over 50% had increased ESR and/or CRP. When measured ($n=23$) P1NP and CTx were increased in a minority (1 and 6 respectively). 58% of patients had a bone biopsy to exclude bacterial osteomyelitis, malignancies or other bone pathology. All received NSAIDs, 22 iv bisphosphonates, 5 methotrexate and 5 anti-TNFα. At time of study median duration of follow up was 6 years (range 1–25), and median age was 17 years (range 11–41). One patient was lost to follow up, 21 were completely asymptomatic, 16 of whom off treatment. Eleven patients had still mild to moderate recurrent symptoms requiring treatment.
Conclusion
CRMO is a rare inflammatory bone disorder associated with variable local and systemic manifestations. The disease presents acutely and responds to treatment

with NSAIDs, and/or iv bisphosphonates or anti-TNFα. In our cohort, long-term clinical outcome of CRMO was good, with over 2/3 of patients being asymptomatic by a median age of 16 years, the majority of whom off treatment. A minority of patients had persistent intermittent mild recurrent symptoms requiring treatment. Further studies are required to identify patients at risk from persistent disease.
Disclosure
The authors declared no competing interests.
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P223

A preliminary data of a prospective study on Iranian patients with osteogenesis imperfecta
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Objectives
Osteogenesis Imperfecta (OI), is a group of rare, heritable disorder of bone and connective tissue. The pathogenicity of OI arises from the mutations in about 17 different genes, involved in collagen type 1 synthesis, processing, post-translational modification, folding, cross-linking, bone mineralization, and osteoblast differentiation. Based on Sillence classification, there are four types of OI; Type I (mild, non-deforming), Type II (perinatal lethal), Type III (severely deforming), and Type IV (moderately deforming). The aim of this study was to collect the preliminary epidemiological and clinical information of Iranian patients with OI
Methods
Sixty-seven of Iranian patients, 42 (62.7%) males and 25 (37%) females) average age: 9.6(, clinically diagnosed as OI patients and classified according to Sillence classification, enrolled into the study for observational investigations and data collection. A questionnaire was designed and the demographic and clinical features of the patients were recorded.
Results
Of 67 OI patients, types IV, III, I, and not identified cases (unknown) were found to be 24%, 30%, 15%, and 31%, respectively. To diagnose the OI type in the latter, more investigations and tests are needed to be done. In most of the patients, the first fractures had occurred between 1 month and 2-year ages (26/67). The rate of consanguineous marriages was found to be almost 64% among which 70% did not have any positive history of OI. Blue/gray sclera was seen in 66% of the patients. 41 cases showed thoracic cage deformity (from mild to severe), and 22 cases had scoliosis/kyphoscoliosis. Forty-seven patients had lower limb deformity, although, the upper limb deformity was seen in 35 patients.
Conclusion
In our preliminary data collection, type III of OI was found to be the most frequent one compared with the other types of OI. Although some of the unidentified cases might change the presented figures after being more analyzed. A higher number of the patients in our study were from consanguineous marriages, whose family did not have any history of OI. This might have an indication of either recessive or novel *de novo* mutations, the definite diagnosis of which requires molecular analysis.
Disclosure
The authors declared no competing interests.
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P224

A teenager with recurrent fractures and multiple bone lesions: a diagnostic challenge
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Background
Ollier disease is a rare sporadic disorder where enchondromas develop close to the growth plate cartilage. Prevalence is around 1 in 100 000. Multiple enchondromas usually develop in childhood. Persons with Ollier disease are prone to pathological fractures. The disease carries a high risk of skeletal, visceral and brain malignancy
Presenting problem
A 14-year-old boy presented with multiple fractures following trivial trauma. He first presented at 11 years with a fracture of his left tibia following a fall at home. At 14 year of age he fractured his left humerus while hanging on a wall with his hands. On examination, he was of average height and weight with no dysmorphic features. He had multiple swellings in fingers of both hands. He had white sclera. There was no family history of bone diseases.
Clinical management
Skeletal survey showed lucent lesions and fractures involving in both upper limbs, lower limbs and pelvis. Both proximal humeral epiphyses were poorly mineralized The appearance was suggestive of multiple enchondromas. Skull X-ray appeared normal. DXA scan showed low bone mineral density (lumbar spine z-score – 1.7, neck of femur z-score – 2.7).
Discussion
The clinicopathological features and pathogenesis of Ollier disease remain controversial. Further, therapeutic options for Ollier disease are limited. However, detecting Ollier disease as early as possible is important to prevent malformations and to monitor for neoplasm development including malignant progression of enchondromas to chondrosarcoma.
Disclosure
The authors declared no competing interests.
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P225

A short girl with severe scoliosis and osteoporosis
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Background
Primary childhood osteoporosis is rare. We report a 9-year-old Sri Lankan girl with severe failure to thrive, scoliosis and low bone mineral density, with no apparent diagnosis.
Presenting problem
A 9-year-old girl was referred for evaluation of short stature and scoliosis. She is the third living child of healthy non-consanguineous parents. She was born at term with low birth-weight (1.8 kg -2.9S.D.), birth length (43 cm, -3S.D.) and head-circumference (30 cm, -3S.D.), and continued to grow poorly. Scoliosis of spine was noted by parents around 3 years of age. She first received medical attention at 6 years of age for a cardiac murmur. Echocardiography revealed an atrial septal defect which was closed surgically at 8 years of age. There was no history of bone pain, backache or fractures. She had recurrent respiratory tract infections, but was not on steroids or any other long-term medication. Family history was unremarkable, except for neonatal death of a sibling, and a short maternal aunt without scoliosis. Her parents and siblings were of normal height. On examination, she had severe growth retardation (height 98.5 cm [-6.3S.D.], weight 9.5 kg [-11S.D.], BMI 9.8 kg/m^2 (-7.7S.D.). She had structural scoliosis with a right thoracic curve, camptodactyly of fingers and lateral deviation of toes. She had normal sclera, no clubbing, nor features of renal disease or rickets.
Clinical management
On biochemical evaluation, she had normal serum calcium (2.3 mmol/l), phosphate (1.47 mmol/l) and alkaline phosphatase (200 IU/l), mild vitamin-D insufficiency (25-OH-D 58.9 mmol/l), normal venous blood-gas-analysis (pH 7.41, bicarbonate 29 mmol/l). Serum IGF-1, full blood count, blood film, serum albumin, liver function tests, serum electrolytes, serum creatinine and stool report were also normal. Spinal X-rays showed scoliosis, and DXA scanning showed very low bone mineral density of lumber spine (z-score-4.4) and hip z-score-4.1).
Discussion
We are looking for a unifying diagnosis, feasibility of surgery for scoliosis and place of bisphosphonate therapy in this child.
Disclosure
The authors declared no competing interests.
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P226

The experience of canakinumab in 2 patients with primary tumor (tumoral) calcinosis

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Background
Primary tumoral calcinosis is an orphan disease. The data about the incidence of this disease, as well as clinical recommendations for treatment are not presented in the literature.
Presenting problem
Two patients – 11.5 years old boy and 8 years old girl with primary tumoral calcinosis had multiple foci of the subcutaneous calcification, walking impossibility, wheel-chair condition, fatigue, high fever and equinus deformity of the left foot. The patient did not have changes in the calcium-phosphorus homeostasis. The boy had increased C-reactive protein (CRP), more than 200 mg/l (normal value <5 mg\l) and the girl had normal CRP under the corticosteroids. Both patients initially were evaluated as juvenile dermatomyositis and he has been received steroids with methotrexate during years without improvement. The efforts to decrease the steroids provoked fever and elevation of CRP in both. Immunological studies ruled out inflammatory myopathies and other rheumatic conditions. Genetic studies for *GALNT3*, *FGF23* and *Klotho* genes were done but did not find any specific mutations. The whole-exome sequence was also done but did not find mutations. The morphology assay was identified as typical changes for tumoral calcinosis.
Clinical management
After verification of the diagnosis, the therapy with an interleukin-1β inhibitor – canakinumab: 4 mg/kg every 4 weeks for boy and every 8 weeks for the girl was prescribed. During the treatment in children, the corticosteroids were discontinued without flares, a significant improvement in the patient's general condition was observed, a decrease in the number of calcinates, and a reduction in inflammation. All children could walk without any support. The boy had a surgery due to deformity of the left foot which was caused by calcification of the Achilles tendon and gastrocnemius muscle without exacerbation
Discussion
The use of an inhibitor of interleukin-1β as a permanent therapy of primary tumoral calcification allowed to control calcification and improve walking and general condition. This work supported by the Russian Foundation for Basic Research (grant no. 18-515-57001).
Disclosure
The authors declared no competing interests.
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Late Breaking Abstracts

LB1

Genetic inactivation of osteocalcin in Col1a1Jrt/+ mice, a model of dominant osteogenesis imperfecta, restores glucose metabolism to wild-type levels

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Objective
Osteocalcin, an osteoblast-derived hormone, is among the most abundant proteins in bone and is involved in the regulation of whole-body metabolism, muscle adaptation, and reproduction. High bone turnover and low bone mass are clinical hallmarks of Osteogenesis Imperfecta (OI), a bone disease mainly caused by mutations in the collagen-I gene. Recently, we have shown that growing mice with a severe dominant form of OI, Col1a1Jrt/+ mice, displayed significantly elevated serum levels of undercarboxylated osteocalcin (uOCN) along with an altered glucose/insulin metabolism and energy expenditure. Further, these mice are protected against high-fat diet induced obesity but not insulin resistance. To further confirm the role of uOCN, we crossed Col1a1Jrt/+ mice (OI) with mice lacking one or both osteocalcin genes (OCN+/−, OCN−/−) to generate OI/OCN mice.
Methods
At 4 and 8 weeks of age, wild-type (WT/WT) and OI/OCN mice were phenotypically characterized and random glucose (RG) measurements along with glucose tolerance (GT) test were performed.
Results
To generate OI/OCN mice, fertile OCN+/− and OI mice were used. Within the first generation, about 27% of generated mice were WT/OCN+/−, 24% OI/WT, 26% OI/OCN+/−, 22% WT/WT, and 1% were found dead. For further breeding, OI/OCN+/− mice were used and gave birth to pups with a genetic distribution of about 18% OI/OCN+/− or WT/OCN+/−, 21% OI/OCN−/−, 12% WT/OCN−/−, 6% OI/WT, and 12% were found dead. Compared to WT/WT, 4-week old mice harboring the genotype OI/WT, OI/OCN+/−, and OI/OCN−/− were smaller in size and up to 20% lower in body mass which declined to about 15% difference at 8-weeks of age. At 4-weeks of age, OI/OCN+/− and OI/OCN−/− mice exhibited lower RG levels than WT/WT littermates ($P<0.05$). However, only OI/OCN+/− mice revealed improved GT ($P<0.01$) while OI/OCN−/− mice did not differ from WT/WT. At 8-weeks of age, no significant differences in RG or GT were found in OI/OCN+/− or OI/OCN−/− mice compared to WT/WT.
Conclusion
Here we show for the first time that knock-out of both osteocalcin genes restored glucose tolerance to WT levels in mice with severe dominant OI, strongly supporting the causative role of osteocalcin driving alteration in glucose/insulin metabolism in OI mice.
Disclosure
The authors declared no competing interests.

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LB2

Lumbar spine quantitative computed tomography (QCT) is a better predictor of vertebral fracture in boys with Duchenne muscular dystrophy (DMD) than either DXA or peripheral QCT

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Objectives
Vertebral fractures are common in boys with DMD taking daily corticosteroids. Treatment is usually initiated when vertebral fractures have been identified. However, prophylactic treatment may be possible if reliable risk factors for vertebral fracture can be identified. The aim of this work was to compare the diagnostic accuracy of three different bone strength assessment techniques in a cohort of DMD boys.
Methods
Thirty-three boys with DMD (mean age = 8.3 (s.d. 2.3) years) were followed over 3.4 (s.d. 1.8) years. All boys had size adjusted lumbar spine DXA (BMAD), distal radius peripheral QCT (pQCT) and axial QCT at baseline and DXA and pQCT at follow-up. Lateral spine imaging was performed to identify incident vertebral fractures. Mobility status and cumulative corticosteroid (CS) exposure were also recorded. Logistic regression analysis was used to identify significant predictors of vertebral fracture and diagnostic testing using a threshold of $Z \leq -1.0$ and or age >8 years was performed with all baseline values.
Results
At baseline 31/33 boys were mobile. During follow-up 20 boys sustained 48 mild and 7 moderate vertebral fractures and 13 boys remained fracture free (FF). There were no differences in cumulative CS exposure, height, weight or body mass index SDSs but boys who remained fracture free at follow up were on average 2.1(0.7) years younger than those who suffered a vertebral fracture (VF), $P=0.02$. There were no significant differences in baseline or follow up LS BMAD or distal radius pQCT bone densities. In contrast, VF boys had a 1.1(0.4) s.d. lower QCT Z-score than FF boys at baseline, $P=0.005$. Logistic regression demonstrated that QCT Z-score was the only significant bone predictor of fracture (Exp(B) = 0.4, $P=0.01$). However, age alone, regardless of bone density, was the strongest overall predictor of future fracture (Exp(B) = 1.9, $P=0.02$).
Conclusion
Axial QCT is the best predictor of vertebral fracture in boys with DMD taking daily corticosteroids. Given, the progressive nature of the disease and prolonged exposure to corticosteroids, it is not surprising that age was the strongest overall predictor of fracture. However, using QCT in combination with age may be a more robust approach when considering prophylactic treatment of vertebral fractures in this population.
Disclosure
The authors declared no competing interests.

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LB3

CD64: An adjunct to Kocher's criteria to differentiate septic arthritis and transient synovitis in children

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Objectives
To make a prediction model for septic arthritis on the basis to analyze CRP versus CD64 on neutrophils (nCD64) as an adjunct parameter to Kocher's criteria to differentiate septic arthritis from transient synovitis.
Methods
In this open ended prospective study, children ($n=34$) below 18 years of either gender (M = 22/F = 12) below 18 years presenting with acute, new onset, non – traumatic limp or joint pain were enrolled as cases and otherwise normal age-sex matched children as controls ($n=35$). Full clinical work up including Kocher's criteria [Non weight-bearing; Temperature; Erythrocyte Sedimentation Rate (ESR) [Wintrobe method] and Total Leucocyte count (TLC) [Automated blood count] in addition to C-reactive protein (CRP) [CRP Turbilatex K LABKIT] and CD64 count on neutrophils (nCD64) [Fluorescence-activated cell sorting (FACS)] were done as per standard protocols and were analysed. Blood sample (2 ml) in plain/EDTA viol was collected at forenoon for lab work. High resolution sonography of joint was done to confirm presence or absence of joint effusion (if no effusion, excluded). Arthrocentesis done as per standard protocol under aseptic technique in effusion positive cases. The cases were divided into septic arthritis (polymorph > 50 000 cells/mm^3) and transient synovitis (polymorph < 50,000 cells/mm^3).
Results
We analyses 35 cases [septic arthritis ($n=18$), transient synovitis ($n=13$)] and controls ($n=35$). No statistically significant differences were found between demographics of cases and controls. Statistically significant differences were found in parameters like temperature, ESR, CRP, TLC and nCD64 count between cases and controls (<0.0001). In cases, except the nCD64 count ($P=0.0079$), all the four Kocher's criteria tests showed insignificant difference between septic arthritis and transient synovitis cases. The sensitivity, specificity and Area under curve (AUC) for nCD64 count were maximum and were 0.50, 0.88 and 0.75 respectively. Addition of nCD64 count in Kocher's criteria had increase their sensitivity, specificity and AUC from 0.30, 0.62 and 0.57 to 0.65, 0.93 and 0.95 respectively.
Conclusion
The CD64 count on neutrophils (nCD64) was the potential diagnostic test for septic arthritis and addition of nCD64 count in Kocher's criteria may increase its reliability. This study will be very beneficial in clinical setup and public health in upcoming future.
Disclosure
The authors declared no competing interests.

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LB4

Impact of pubertal suppression on body composition and bone density in adolescents with gender dysphoria

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Introduction
Pubertal suppression with gonadotrophin releasing hormone (GnRH) analogue is introduced after onset of puberty in adolescents with gender dysphoria (GD). As puberty is a critical period for bone accrual and changes in body composition, alterations in body composition and bone mass may be observed during treatment.
Methods
Thirty-eight adolescents (32/38 assigned females at birth) with GD had dual energy X-ray absorptiometry (DXA) prior to starting GnRH analogue and after one year of therapy. DXA lean mass index (LMI:defined as DXA lean mass/height2) and fat mass index (FMI: defined as DXA fat mass/height^2) were converted to *Z*-scores based on LMI and FMI centiles from a cohort of healthy children from Glasgow. DXA total body less head bone mineral content (TBLH-BMC) and DXA lumbar spine bone mineral apparent density (LS-BMAD) were converted to *Z*-scores based on UK normative data. TBLH-BMC was adjusted for lean mass, fat mass, height, age and ethnic background.
Results
Median age at baseline was 14.2 years (10.6,15.7) with 33/38 (87%) in late puberty (Tanner IV and V). Median body mass index (BMI) *Z*-score, at baseline and after one year of treatment, was $+0.9(-1.7,+3.4)$ and $+1.4(-0.8,+3.5)$, respectively [$P<0.0001$]. Median FMI *Z*-score, at baseline and at one year, was $+0.8(-1.1,+2.1)$ and $+1.0(-0.1,+3.2)$, respectively [$P<0.0001$]. Median LMI *Z*-score was $-0.6(-2.8,+2.6)$ at baseline, and $-0.7(-3.6,+1.5)$ at follow-up [$P<0.0001$]. Twelve months of pubertal suppression led to reduction of LS-BMAD *Z*-score, from median of $-0.1(-2.2,+2.3)$ at baseline to median of $-0.5(-2.7,+1.8)$ at 1 year [$P<0.0001$]. Similarly, median TBLH-BMC *Z*-score was $+0.4(-2.6,+3.6)$ at baseline, and $+0.2(-2.8,+2.9)$ at follow-up, [$P=0.03$]. LS-BMAD *Z*-score was positively associated with baseline LMI *Z*-score [$r=0.43$, $P=0.007$] and follow up ([$r=0.47$, $P=0.003$]. In those adolescents (n, 8) who showed a reduction of >1.0 S.D. in LS-BMAD *Z*-score between baseline and one year, median change in LMI *Z*-score was $-1.1(-1.5,+0.2)$ compared to median change in LMI *Z*-score of $-0.2(-1.2,+2.7)$ in those with a reduction of <1.0 S.D. in LS-BMAD *Z*-score between [$P=0.003$].
Conclusion
Adolescents with GD have relatively low lean mass and relatively high fat mass at baseline. After one year of treatment with GnRH analogue, they showed further reduction in lean mass, an increase in fat mass and a reduction in bone density, at both lumbar spine and total body.
Disclosure
The authors declared no competing interests.

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LB5

Chronic recurrent multifocal osteomyelitis in children with hypophosphatasia explained by anti-inflammatory nucleotidase activity of tissue nonspecific alkaline phosphatase in mesenchymal and hematopoietic cells

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Deficiency in tissue nonspecific alkaline phosphatase (TNAP) causes hypophosphatasia (HPP), which is mainly characterized by skeletal hypomineralization. TNAP promotes mineralization by dephosphorylating the mineralization inhibitor inorganic pyrophosphate (PPi), which is generated from adenosine triphosphate (ATP) by ectonucleotide pyrophosphatase phosphodiesterase 1 (NPP1). Chronic recurrent multifocal osteomyelitis (CRMO), a sterile bone auto-inflammatory disease, has been described in childhood HPP (Girschick, BMC Pediatr 2007), but how TNAP deficiency triggers CRMO remains unknown. Interestingly, several chronic non-bacterial osteomyelitis related monogenic auto-inflammatory diseases rely on pathological IL-1β activation. Deficiency of IL-1 receptor antagonist (DIRA) or cryopyrin-associated periodic syndrome (CASP, NLRP3 activating mutations) generate IL-1β-associated osteomyelitis. Since NLRP3-dependent secretion of IL-1β relies on extracellular ATP release and autocrine binding to purinergic receptors, we hypothesized that CRMO in HPP children is due to the lack of extracellular ATP dephosphorylation by TNAP and pathological activation of NLRP3. We first observed by quantitative PCR that bones from 7-day-old Tnap+/− mice presented increased levels of Il-1β and Il-6 and decreased levels of the anti-inflammatory Il-10 cytokine as compared with Tnap+/+ mice. Tnap levels were higher than those of the nucleotidases Npp1, Cd39 and Cd73 in bones of WT 7-day-old mice, as well as in primary mouse osteoblasts and hypertrophic chondrocytes. In these cells, TNAP inhibition with MLS-0038949 exacerbated IL-6 production in response to pro-inflammatory signals. This was accompanied by decreased hydrolysis of ATP and AMP. We however observed that mouse and human mesenchymal cells are unable to activate IL-1β in response to ATP. Since NLRP3 activation in myeloid cells but not in mesenchymal cells was reported to induce osteomyelitis (Wang, Sci Rep 2017), we explored the function of TNAP in neutrophils, which are the leukocytes that have the highest TNAP activity. We found that TNAP inhibition not only exacerbated IL-1β secretion in LPS-activated human neutrophils, but also increased their survival. Collectively, these results demonstrate that TNAP is an anti-inflammatory nucleotidase in mesenchymal cells and neutrophils, and that its deficiency in neutrophils but not mesenchymal cells, is likely to result in pathological IL-1β activation and CRMO.
Disclosure
The authors declared no competing interests.

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LB6

Abstract withdrawn.

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LB7

Validation study of automated bone age assessment in 1285 children and adolescents aged 5 to 16 years

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Background
Skeletal maturation is the most reliable indicator of biological age in children and adolescents. The evaluation of hand and wrist X-Ray according to Tanner-Whitehouse (TW3) or Greulich-Pyle (GP) are the most commonly used methods for biological age assessment. Automated bone age assessment has recently become increasingly popular, however a large independent study comparing automated and manual evaluation of bone age is still missing. The aim of this study was to assess the differences between automated and manual evaluation of bone age using TW3 and GP method.
Methods
In this cross-sectional study we evaluated bone age scans using TW3 and GP methods in 1285 children and adolescents (659 boys, range 5.0–15.9 years, median 10.3, IQR 4.9 years) with various endocrine conditions in parallel manually and using BoneXpert software (version 2.4.5.1). Root mean square errors (RMSE) were calculated for the whole group and for sex-specific one-year age categories (girls 5–15 years, boys 5–16 years, over 50 children in each category).
Results
In total RMSE were 0.61 years and 0.58 years in boys and 0.79 years and 0.60 years in girls, respectively for TW3 and GP. Sex- and age-specific analysis

showed the greatest differences between manual and automated TW3 evaluation in girls between 6–7, 12–13 and 13–14 years with RMSE 0.90, 0.90 and 1.05 years, respectively. Manual and automated evaluation differed by more than 1 year in 9.7% and 7.0% boys and 18.2% and 8.6% girls, respectively for TW3 and GP. In more detailed analysis of the TW3 method RMSE showed improvement (RMSE for boys 0.54; for girls 0.71), after the exclusion of X-Rays where stages for radius and ulna assigned by BoneXpert significantly differed from the definition set by Tanner and Whitehouse.
Conclusion
Automated bone age assessment provides sufficient agreement with manual evaluation in most scans of children with common endocrine disorders. Bone age assessment provided by BoneXpert tends to be underestimated, especially in girls during puberty using TW3 method. The greatest emphasis in the TW3 method is put on the radius and ulna evaluation, differences in assigned stages can therefore be a source of discrepancies between manual and automated rating.
Disclosure
The authors declared no competing interests.

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LB8

Abstract withdrawn.

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LB9

Monitoring skull base abnormalities in children with osteogenesis imperfecta

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Objectives
In the context of a lack of national consensus, the aim of this study was to identify the clinical impact of skull base imaging in children with osteogenesis imperfecta (OI).
Methods
A retrospective review was conducted of case-notes and radiological images of children with severe, complex and atypical OI at a designated specialist centre, between 01/2012 and 08/2018. Patient demographics, clinical features at time of imaging and radiological parameters (Wormian bones, platybasia, basilar impression (McGregor's technique) and basilar invagination (McRae's technique)) were recorded and correlated.
Results
Of the 127 patients, 33 were excluded due to absence of imaging. A total of 321 radiographs and 39 MRI scans of 94 patients (52% males) were analysed. Prevalence of radiographic abnormalities was, Wormian bones 59/94(62.8%), platybasia 58/94(61.7%), basilar impression 10/94(7.1%) and basilar invagination 1/94(1.1%). Platybasia, basilar impression and basilar invagination could not be measured in 71/321(22.3%), 48/321(14.8%), and 33/321(19.6%) radiographs respectively (reasons included poor positioning, anatomical abnormalities and poor image quality). Of the 23 radiographs with basilar impression, 17(85%) also had platybasia while 3(13%) did not ($P=0.04$). Wormian bones had equal prevalence in patients with and without basilar impression. Prevalence of skull base abnormalities on MRI was basilar impression 23(58.9%), basilar invagination 9 (23.0%) and abnormal spinal cord signal, CSF flow or cerebellum 14(35.9%). There was a lack of concordance between MRI and matched radiographs in 22.2% (4/18), 35.7% (5/14) and 14.3% (2/14) for platybasia, basilar impression and basilar invagination respectively. Fewer than 5% had positive clinical symptoms or signs at the time of their radiographs; (2.1%(7/321) had macrocephaly, 0.6% (2/321) headache, all other neurological features were absent). However, these features were not documented in $>85\%$ of cases.
Conclusion
There is 1) a low prevalence of neurological symptoms and skull base abnormalities and 2) poor concordance between MR and radiographic skull base parameters in children with OI. Although it may reflect their absence, neurological symptoms and signs are not routinely documented. A prospective study is required to produce data to inform the development of national guidelines for skull base imaging in OI.
Disclosure
The authors declared no competing interests.

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LB10

Foramen magnum stenosis (FMS): neuroradiological aspects before and after cervical decompression in paediatric patients with achondroplasia (ACH)

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The identification of markers indicative of pathological FMS plays a pivotal role in the prevention of ACH complications.
Objective
Identify key cranio-cervical junction neuroradiological features for the surgical choice and for the decompression outcome.
Methods
Out of 191 ACH patients, we selected 24 patients before 4 years of age, who performed a first brain MRI and/or CT. Patients were divided into 2 groups: surgically treated (STP = 15/24) and no-surgically treated (NSTP = 9/24). Data were compared with a control group (CG) of 24 children of the same age and with a group of ACH patients surgically treated at an age above 4 years (ACHPST > 4 years 5/191). Antero-posterior cervical osteo-ligamentous diameter (APCOL-D), anteroposterior cervical bone diameter (APCB-D), degree of cervical stenosis (grade:0 to 3, defined on the basis of the increase in stenosis and grade 4A and 4 B according to the degree of stenosis plus myelopathy1), prominence of posterior margin foramen magnum (PFMPM), prominence first cervical vertebra posterior arc (PFCVPA), hypertrophy of soft tissues, occipital bone spur, orientation of the posterior edge of the foramen magnum, odontoideum bone were evaluated by MRI.
Results
12/24 subjects performed the first MRI in the first 6 months of life and 4/12 have myelopathy (stenosis 4A and 4B). All STP have cervical stenosis of grade >2, while the NSTP have degrees <2. Grade 1 is equally represented in STP and NSTP. The APCB-D is decreased in the STPvsCG ($P\leq0.0001$) and in the NSTPvsCG ($P\leq0.001$); there is no significant difference between STPvsNSTP. APCOL-D is decreased in the STPvsNSTP, STPvsCG ($P=0.0001$) and NSTPvsCG ($P=0.001$), with an OR = 3.95 ($P=0.02$, values <7.6 mm determine a risk of surgical therapy 4 times higher). PFMPM is associated with surgery ($P=0.003$), while no other qualitative parameters are significantly associated. In STP there is an increase of APCOL-D and APCB-D ($P=0.0001$).
Conclusions
MRI screening role was confirmed, and highlighted its role in the first 6 months of life. The most important parameters for surgical choice are: PFMPM, APCOL-D, the degrees of stenosis >2. STP have a good radiologic decompression outcome. The data of this pilot study will be correlated with multidisciplinary approach, useful particularly for evaluation of grade1 stenosis (gray area regarding surgery)
Disclosure
The authors declared no competing interests.

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Author Index