

14TH INTERNATIONAL CONFERENCE
ON OSTEOGENESIS IMPERFECTA

OI2022

30 AUGUST - 2 SEPTEMBER 2022

SHEFFIELD, UK

ABSTRACTS



www.oi2022.org

The 14th International Conference on Osteogenesis Imperfecta was held in Sheffield from 30 August to 2 September, 2022. The conference provided an opportunity for all those engaged in research and clinical practice in the field to come together and share experiences and their latest data. Originally scheduled to take place in 2020, it was delayed, as so many similar events were, by the Covid pandemic. A total of 290 delegates registered and 124 abstracts were accepted as posters with a further 31 oral communications. A total of 14 abstract authors were selected for ICCBH-ECTS New Investigator Awards. This is the largest number of delegates and abstracts for any of the meetings in this series, attesting both to the vibrancy of the field currently, and the pent-up demand to interact with fellow professionals.

The main meeting was preceded by an ERN BOND-sponsored workshop on early life interventions and assessments, and a presentation and discussion of the rehabilitation in OI consensus document.

For the main meeting there was a very wide-ranging program including presentations from patient groups, basic and clinical researchers, allied health professionals, practising physicians and surgeons, geneticists and radiologists.

The basic and clinical science program showcased the range of activity in the field with a clear focus on translation to the human experience of OI. There specific sessions on molecular mechanisms and cellular disturbance; a lively debate on the utility of animal models and the difficulties of translation into human studies; a specific round table on current and proposed interventional clinical trials; and a session on the delivery of services in different healthcare settings.

Surgeons had the opportunity through “hands-on” workshops to access the latest hardware and instruments, see and participate in demonstrations of their use and network to share advances in techniques and approaches. The importance of preparation and post-operative rehabilitation was a clear focus for workshop participants, including those from a therapy background.

A symposium sponsored and organised by Mereo BioPharma focused on the key manifestation of OI – fractures – linking tissue properties in both normal and abnormal bone with current fracture detection technologies. A report on the symposium is included in this publication.

The main conference dinner was held in the Sheffield Cathedral where guests were addressed by Lord Kevin Shinkwin, a British peer who has OI and who was able to attest to the impact of research and clinical advances on his own health and well-being.

The conference was supported by a broad range of sponsors and other supporters, including patient advocacy groups and other professional societies and groups.

Feedback from the meeting has been extremely positive with many delegates citing the broad range of activities and opportunities as being really important to them.

The next meeting will be held in Hong Kong in 2025, with the local organiser being Dr Michael To.

Nick Bishop (Sheffield, UK)

14th International Conference on Osteogenesis Imperfecta

Meeting Chair

Organisers

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janet@janet-crompton.com

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Statements and descriptions are informational only and are not made or given as a warranty. The views, opinions and statements made at the conference are solely those of the presenters and may not reflect the views of the Organisers. Furthermore, participants should bear in mind that presenters may have vested interests in the concepts and products they discuss.

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ICCBH-ECTS New Investigator Awards

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

Nati Alcorta (Barakaldo, Spain) OC20

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Lauria Claeys (Amsterdam, Netherlands) P87

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Milena Jovanovic (Bethesda, USA) OC6

Kyle Kavaseri (Montreal, Canada) OC28

Raissa Passos dos Santos (Montreal, Canada) P102

Alice Stephan (Cologne, Germany) OC10

Chen Zhang (Amsterdam, Netherlands) OC19

IS1

What can the osteogenesis imperfecta community learn from other diseases: Duchenne exon skipping and gene therapy approaches

Annemieke Aartsma-Rus

Leiden University Medical Center, Leiden, Netherlands

ABSTRACT

Mutations in the dystrophin gene underlie both the severely progressive Duchenne muscular dystrophy (DMD), and the later onset and slower progressive Becker muscular dystrophy (BMD). Normally, dystrophin connected the intracellular contractile machinery to the connective tissue surrounding each muscle fiber. DMD patients have mutations that disrupt the production of functional dystrophin, while BMD patients have mutations that maintain the open reading frame and allow production of internally deleted, but partially functionally functional dystrophin proteins.

Different therapeutic strategies are in clinical development to restore dystrophin production, with the exon skipping and micro-dystrophin gene therapy approaches being the most advanced. Exon skipping aims to modulate the pre-mRNA splicing of DMD dystrophin transcripts to enlarge the deletion but restore the open reading frame, so that a BMD-type dystrophin can be produced. This approach utilizes antisense oligonucleotides (ASOs), short pieces of chemically modified RNA that hybridize specifically to specific exons. ASO-mediated exon skipping is a mutation specific approach, meaning that different ASOs need to be developed for different groups of patients. Delivery of the ASOs to the target tissues (skeletal muscle and heart) is currently challenging, but 4 ASOs have received FDA approval for Duchenne patients based on very low dystrophin restoration (~1%). Whether this has functional effects needs to be assessed in ongoing clinical trials.

Gene therapy for DMD relies on the only viral vector able to efficiently infect skeletal muscle, the adeno-associated virus (AAV). A minimalistic approach was needed to narrow down dystrophin to its more crucial domains in order to come to a cDNA that fits within the AAV vector (~4.5 kb). Body-wide delivery is possible but this is associated with severe side effects due to high doses needed. Whether the micro-dystrophin is functional in humans is not yet known.

In this lecture I will outline the challenges and opportunities but also lessons learned from developing these approaches for DMD and how the OI field can potentially benefit from this.

IS3

Registries for osteogenesis imperfecta: where we are and where we are heading

Muhammad Javaid

University of Oxford, Oxford, United Kingdom

ABSTRACT

There are multiple registries for rare bone diseases including osteogenesis imperfecta within and between countries. The registries have been developed to fulfil the needs of different stakeholders, including patient groups, patients, clinicians, researchers, decision-makers and regulators. Clearly defining the primary purpose of a registry is crucial for the content, format/ interface and its regulatory framework. The role of registries in the clinical and research environment also has to take into account the increasing use of electronic healthcare records and the potential of machine learning techniques. In this presentation, we will discuss the examples of registries from patient groups, researchers and clinical communities. We will also discuss the potential challenges and opportunities to building national and international registries going forward.

IS4

Whose life is it anyway? The challenge to include the patient voice in studies of osteogenesis imperfecta

Laura Tosi

Children's National Hospital, Washington, DC, USA

ABSTRACT

The Osteogenesis Imperfecta Foundation has striven to expand the science behind OI care for over two decades. Since 2001, the Foundation has supported Scientific Meetings to support research, and, more recently, Town Hall meetings to support clinical care. The OI Registry, established in 2005, became accessible online in 2014. Leveraging the online capabilities of the PROMIS (Patient Reported Outcomes Measures Information System) initiative in 2011, the Adult Natural History Initiative explored the broad spectrum of both orthopaedic and non-orthopaedic challenges faced by adult OI patients. The OIF then funded the establishment of the Linked Clinical Research Centers (LCRC) from 2009 and 2014 which allowed the collection of preliminary data needed to make the Foundation eligible for an NIH Natural History award. The Brittle Bones Consortium OI Natural History Study is now in its eighth year and has led to numerous publications that have expanded our understanding of the many unique health issues faced by the OI community.

While in the past, investigators used changes in clinical endpoints or laboratory biomarkers to reflect the impact of clinical interventions, more recently, patient input has encouraged researchers to embrace new research endpoints that are more informative about the effect of an intervention on the day-to-day physical and psychological well-being of patients and caregivers. The OIF has responded to this trend by leveraging PCORI (Patient Centered Outcomes Research Institute) awards to explore patient research priorities and increase patient/caregiver capacity to participate in research.

At a time when new therapies that might help patients with osteogenesis imperfecta are proliferating, developing instruments that define outcomes that are most relevant to patients must be a priority. However, this is a daunting undertaking. The US Food and Drug Administration (FDA) guidance on using Patient-Reported Outcome Measures (PROMs) in both common and rare diseases emphasizes the reliability, validity, and feasibility of such measures and their ability to detect meaningful change (responsiveness). To date, few PROMs have been validated in rare disease populations; thus currently their use in clinical trials is limited. Going forward the challenge will be to develop instruments that cover the full spectrum of the OI experience.

IS5

Key4OI project update

Richard Kruse

Nemours Children's Hospital, Delaware, USA

ABSTRACT

Delivery of health care increasingly incorporates both objective clinically reported and subjective patient reported outcome measures to improve quality and value to the patient and the health care system. Worldwide there are diverse patient registries available to attempt capturing outcome measures. However, health care systems, resources, and patient perceptions vary worldwide on the perceptions of needs and goals of a patient with a specific medical condition.

The Key4OI international interdisciplinary working group of 27 members used a consensus-driven modified Delphi approach based on best available evidence to develop a set of global outcome measures for patients with OI. All disciplines involved in care for OI participated as well adults and children with different types of OI were represented.

Patient focus groups were involved to prioritize the outcome domains by taking into account the items important to the OI community.

More than 400 different outcome measures were identified in our literature search. The structure of the International Classification of Functioning, Disability and Health (ICF) was followed to aggregate data.

The ICF is an international classification that describes health conditions:

1. body functions and structure,
2. activities and participation,
3. personal and environmental factors as well as how they are interrelated.

After three Delphi rounds, 24 domains were selected. After the focus group sessions, the number of domains were reduced to 15. A consensus was reached on the measuring instruments to cover these domains for both children and adults. These measures provide a minimal informational data set to collect as part of a robust medical record.

This work was published in Orphanet Journal of Rare Diseases in 2021:

This set of outcomes is recommended for use by interdisciplinary teams caring for people with OI. It is only by agreeing on a standard set of outcome measures for the comprehensive assessment of OI that comparison of outcomes across centers, needed for quality-improvement endeavors, comparative effectiveness research, and value-based healthcare reform can become a reality in the future.

This talk will update the status of implementation of this data set at the involved centers globally.

IS7

Circadian clock regulation of collagen homeostasis

Joan Chang¹, Adam Pickard¹, Antony Adamson¹, Richa Garva¹, Chloé Yeung², Christopher Smith¹, Donald Gullberg³, Karl Kadler¹

¹University of Manchester, Manchester, United Kingdom. ²Copenhagen University Hospital-Bispebjerg and Frederiksberg, Copenhagen, Denmark.

³University of Bergen, Bergen, Norway

ABSTRACT

Collagen-I (hereby referred to as collagen) mutations are the cause of rare diseases including osteogenesis imperfecta. Dysregulation of normal collagen also leads to conditions such as poor wound-healing and fibrosis. Despite collagen's fundamental importance, therapeutics for collagen pathologies have been lacking, due to conceptual hurdles in how collagen is assembled or removed.

We have discovered that collagen secretion is governed by the circadian rhythm, and that disruptions to the circadian rhythm leads to abnormal collagen fibril formation. Additionally, investigation into the fate of collagen endocytosed by fibroblasts, revealed an unexpected endosome-recycling route that feeds into collagen fibrillogenesis, instead of degradation. These findings present new perspectives to how collagen is controlled, and highlights the complexity of such controls. Preliminary data from an endogenously tagged mouse model also indicated a previously-unknown role for the N-propeptide region of collagen, in particular during development.

This talk will provide an overview of collagen-I fibrillogenesis, and summarise our new findings on how this process is controlled by fibroblasts and the circadian rhythm.

This research is funded by Wellcome and UKRI MRC.

IS8

Bone, brain and beyond

Meena Balasubramanian

University of Sheffield, Sheffield, United Kingdom. Sheffield Children's Hospital, Sheffield, United Kingdom

ABSTRACT

Osteogenesis Imperfecta (OI) is the commonest form of heritable bone fragility. OI is predominantly a type 1 collagenopathy caused mainly due to defects in production, processing or secretion of type 1 collagen.

However, there are other conditions that present with unexplained fractures as part of their phenotype. We have a cohort of patients with these disorders and undertaken in-depth phenotyping in this cohort. Individuals within this cohort have pathogenic variants in neurodevelopmental genes with the common theme being these genes

result in a developmental disorder and unexplained fractures over and beyond what we expect in a child with intellectual disability (ID).

It is important to establish underlying cause for fractures and effect on bone health in individuals presenting with intellectual disability and/or seizures and bone fragility. It is unclear how to treat these individuals and what clinical follow-up should be in place. This talk will describe the presenting phenotypes and explore the shared pathways influencing bone and brain development using several clinical examples.

IS9

Psychological well-being in children and young people with osteogenesis imperfecta

Rebecca Jones

Sheffield Children's Hospital, Sheffield, United Kingdom

ABSTRACT

Promoting psychological wellbeing in children and young people with complex health conditions is important and necessary for prevention of secondary mental health problems, poorer outcomes and reduced quality of life (Naylor et al. 2012). Within the NHS England Severe and Complex OI service, at Sheffield Children's Hospital, psychological support alongside multidisciplinary input begins at birth with interventions designed to enhance bonding, play and well-being of infants and parents. This is followed by interventions at different stages of development impacted by the health condition such as hospital related anxiety, mood difficulties, peer relationships and adjustment to condition.

This presentation will provide an overview of issues of well-being and mental health that can be experienced at different points during development by children and young people with OI.

Ideas that can be used by all health professionals to facilitate the delivery of developmentally appropriate advice, support and interventions will then be shared. In long-term conditions psychological well-being is enhanced by considering the interactions between developmental stage, condition and life experience. As such the importance of assessing and understanding developmental stages will be discussed. Examples from clinical practice will also be provided to support the wider medical, nursing and allied health community in providing appropriate preventative and interventional psychological support strategies to children and young people with OI. In addition, theoretical bases for the provision of clinical psychological support and therapeutic models used will be briefly explored with the aim of giving colleagues insight into why psychologists use the approaches that they do to enhance well-being and mental health.

IS10

Transition from child to adult care

Davina Ford¹, Jennie Walsh²

¹Sheffield Children's Hospital, Sheffield, United Kingdom.

²University of Sheffield, Sheffield, United Kingdom

ABSTRACT

Young people at transition from paediatric to adult care have specific needs. They are neither big children nor small adults. They are managing the unique challenges of having a diagnosis of osteogenesis imperfecta in addition to ongoing physical and mental maturation, taking exams, making decisions about their future, navigating friendships and sexual relationships and growing independent from their parents.

A significant number of young people are lost to follow-up during transition, which impacts on their long term health. Surveys of young people find that while they do care about having an age-appropriate environment, their highest priority is having highly competent healthcare professionals.

Families are often apprehensive about transition – the paediatric team have looked after them and their child through difficult situations; they have a lot of faith in them and are fearful of receiving less personalised and compassionate care in adult services.

Successful transition needs planning and preparation, considering medical treatment, therapy, study and work, family support, empowering the young person to express their needs and priorities, and mentorship to learn how to navigate adult health care systems. There are national frameworks and guidance for transition care, which need to be interpreted and applied to each locality and patient group.

In Sheffield the transition process begins at age 12-14yrs. A MDT approach to preparing the adolescent is offered through age-banded clinics or during admission for bisphosphonate infusions. The young person meets familiar AHPs without parents, prior to their consultant appointment. A locally developed checklist is used to initiate age- and disease-appropriate conversations. With parents involved, a target date for transfer to adult services is worked toward.

At transition clinic, the adult doctor meets the young person and their carers in the paediatric clinic. We think that patients seeing the trust between the paediatric and adult team is crucial in our transition process. The transition is supported with welcome letters from the adult clinic and a pre-clinic phone call from a support worker.

At the first appointment in the adult clinic, we review the whole history, discuss the services available, and open the door to conversations about pregnancy and genetic counselling.

IS11

Sleep

Ruth Kingshott

Sheffield Children's Hospital, Sheffield, United Kingdom

ABSTRACT

Sleep, and breathing adequately during sleep, are fundamental physiological needs. This talk will begin with a basic overview of sleep physiology and how sleep restriction and fragmentation affect health and wellbeing. It will then discuss some of the potential sleep and breathing issues in individuals with OI. Work will be presented on focus groups with young people with OI and sleep questionnaire data. The final part of the talk will discuss what sleep and breathing investigations are available and data from a pilot study examining potential sleep and breathing complications in children and young people with OI. The talk will end with how to include sleep and breathing assessments in clinical practice.

IS15

Collagen processing and endoplasmic reticulum stress

Elena Makareeva¹, Laura Gorrell¹, Shakib Omari¹, Satoru Otsuru², Sergey Leikin¹

¹National Institutes of Health, Bethesda, MD, USA.

²University of Maryland, Baltimore, MD, USA

ABSTRACT

Misfolding of collagen with Gly substitutions causes over 80% of severe OI cases, but it has remained unclear how osteoblasts (OBs) handle the misfolded molecules and their accumulation in the Endoplasmic Reticulum (ER). Our studies of G610C mice with a Gly610Cys substitution in the triple helical region of the $\alpha 2(I)$ chain of type I collagen revealed ER disruption and cellular stress in OBs *in vivo* and *in vitro* yet no unfolded protein response (UPR) underlying canonical ER stress. Similar cellular responses were observed in cultured fibroblasts from some OI patients, yet UPR was detected in fibroblasts from other patients and hypertrophic chondrocytes from G610C mice. To understand this cellular stress variability, mechanism, and role in OI, we combined live cell imaging, single cell transcriptomics, mRNA-based histology, and biochemical approaches to investigating mouse OBs *in vivo* and *in vitro*, revealing unexpected procollagen handling by the cells. Like all secretory proteins, procollagen precursor of collagen is folded in the ER and exported through ER exit sites (ERESs). Its triple helix misfolding, however, is not detected by BIP or other chaperones in the ER lumen. Because of the unique sequence and structure of the triple helix, its quality control occurs at ERESs rather than in the ER

lumen. Misfolded procollagen is retained at ERESs, triggering direct ERES engulfment and degradation by lysosomes (microautophagy). Blockage and depletion of ERESs causes accumulation of procollagen and other proteins in the ER lumen, which is still not detected by ER lumen chaperones. Instead, the integrated stress response (ISR) of the cell appears to be activated by disruption ER-mitochondria contacts, reducing the misfolded protein load in the ER through upregulation of protein degradation and downregulation of protein translation. Disruption of the osteoblast ER by accumulating proteins activates a mitochondrial ISR branch mediated by mt-HSP70 and ATF5. The latter are mitochondrial paralogues of the canonical ER stress mediators BIP and ATF4, respectively. When this response is not sufficient, more severe ER disruption leads to secondary misfolding of globular proteins, BIP sequestration, and secondary UPR, explaining the ISR with and without the UPR and suggesting novel therapeutic targets.

IS16

Osteocyte and pulmonary changes in mouse models of OI: a transcriptomic approach

Roy Morello

University of Arkansas for Medical Sciences, Little Rock - AR, USA

ABSTRACT

We are interested in poorly studied aspects underlying the pathogenesis of osteogenesis imperfecta (OI), the most commonly inherited bone fragility disorder, caused by alterations in type I collagen. For instance, because type I collagen is the most abundant matrix component secreted by bone forming osteoblasts, these cells have been considered the primary mediators of the disease presentation. Consequently, the specific role of osteocytes in the dramatic skeletal manifestations of OI has largely been overlooked. Moreover, although type I collagen is expressed in most tissues, including the lung, the potential effects of type I collagen mutations in causing respiratory distress at birth and a decline in respiratory function, two leading causes of mortality in patients with OI, are not well understood. Therefore, we investigated osteocyte and pulmonary changes in mouse models of OI. First, we genetically ablated RANKL expression in osteocytes in the oim/oim mouse model of OI and observed significant rescue of their bone mass. Second, we found that the osteocyte transcriptomes from 2 mouse models of OI, oim/oim and CrtpKO, were significantly dysregulated compared to control mice, with several differentially expressed genes involved in important processes such as collagen processing, cell adhesion, and cell signaling pathways. These data suggest that osteocytes may play an unrecognized role in the pathogenesis of OI. We have also performed lung histology, histomorphometry, respiratory mechanics, and spirometry-like measurements in oim/+, Col1a2+/G610C, CrtpKO, and oim/oim mouse models of OI. All of them showed alveolar simplification and reduced alveolar surfaces accompanied by changes in their respiratory mechanics parameters that clearly correlated with the degree of their emphysematous changes and the severity of their skeletal phenotype. Sexual dimorphism was also evident, with female mice on average having less severe respiratory changes compared to male mice. Current studies are aimed at better understanding cellular and molecular changes in the lung of CrtpKO mice using spatially resolved and single-cell RNA sequencing.

IS19

Acetabular protrusion and its clinical implication

Mi Hyun Song, Norazian Kamsan, Tae-Joon Cho

Seoul National University Children's Hospital, Seoul, Korea, Republic of

ABSTRACT

Osteogenesis imperfecta has been known to develop acetabular deformity, which has long been described as protrusio acetabuli (PA) based upon the appearance on plain radiograph. However, on 3D-CT images taken for unexplained hip pain in an OI patient, we noted an acetabular deformity different from classical PA. Hence, we reviewed 3D-CT images of the pelvis in 40 hips of 20 OI patients, which were

taken for various purposes. Ten of 40 hips had classical PA, while 17 of them had acetabular deformity different from PA although they appeared to be PA on plain radiograph. We named it as pseudo-protrusio acetabuli deformity (PPAD). PPAD was characterized by the findings that the acetabular segment rotated upwardly and medially, the femoral head center migrated superiorly, and the femoral head was uncovered anteriorly. We also reviewed plain radiographs of 295 OI patients, who were older than 5 years, and did not have pelvis fracture - 133 Sillence type I, 96 type IV, 53 type III, and 13 type V. Hip joints with center-edge-angle > 40 degrees were selected as deformed acetabulum. Incidence of deformed acetabulum was significantly associated with the severity of OI - 2.3% of hips in Sillence type I, 15.6% in type IV, and 62.0% in type III ($p < 0.001$). Among the radiographic findings analysed, the most characteristic pattern of PPAD was superomedial bulging of the iliopectineal line (sensitivity 73.3%, specificity 100%). This finding was observed in 31 of 96 hips with deformed acetabulum - in 3 hips of Sillence type IV and 28 hips of type III. This study showed that acetabular deformity is common in OI patients, associated with the severity of disease. Substantial number of hips showed PPAD, which may not cause acetabular impingement but anterior uncovering and hip instability can be an issue. Superomedial bulging of the iliopectineal line suggests this pattern of acetabular deformity.

IS20

Muscle in osteogenesis imperfecta: all that's brittle is not bone

Alex Ireland

Manchester Metropolitan University, Manchester, United Kingdom

ABSTRACT

Whilst the skeletal impacts of osteogenesis imperfecta (OI) are most commonly highlighted, other tissues – particularly those with a substantial collagen content – are also affected. One such tissue is muscle, whose health influences participation in education, employment and recreation. Poor muscle health and function is also a key risk factor for important clinical outcomes including premature mortality and functional decline. Therefore muscle deficits in individuals with OI have important consequences for health and wellbeing across life. This talk will summarise current knowledge and research gaps in this area, a brief overview of which is given below.

Substantial deficits in multiple components of muscle function including balance, strength, power and endurance have been reported in children and adolescents with OI. This has important consequences for health-related quality of life, with the majority of adults with OI reporting problems with mobility and activities of daily living. Studies have largely focused on individuals with OI type I, and relatively little is known about muscle function in adults with any OI type. Muscle function deficits in individuals with OI appear to result from a combination of reduced muscle size and quality. Potential underlying mechanisms include mitochondrial dysfunction and paracrine signalling, in addition to impaired collagen quantity and quality and the contribution of lifestyle factors such as physical activity. Whilst some of these factors have been explored in animal studies, there is limited information on their contribution to muscle health in humans. A small number of studies have investigated the effects of exercise, pharmacological and genetic interventions on muscle, although none in adults. Therefore important gaps remain in our characterisation of muscle deficits in OI, in addition to the underlying pathophysiology and potential treatments.

IS22

Brittle bones and neurones - neurological aspects of Osteogenesis Imperfecta

Catherine DeVile

Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom

ABSTRACT

Osteogenesis Imperfecta (OI) is a multi-system disorder characterised by primary bone fragility which can affect the nervous system both central and peripheral, either as a direct association of the condition, or due to secondary complications from fractures and injury.

Cranial complications may include abnormalities of the skull and skull base and although the prevalence of radiologically identified basilar invagination in children is low, 4% across a national Highly Specialised Service (HSS) in England, neurological symptoms when present are significant and treatment options complex. A risk stratification approach and clinical algorithm for monitoring of skull base abnormalities in children is currently implemented across the HSS in England.

Rarely, there are abnormalities of brain parenchyma on neuroimaging, such as cerebellar hypoplasia or more generalised cerebral atrophy with ventriculomegaly, as well as trauma-related pathology, such as skull fractures and intracranial haemorrhage. In children, it is important to consider and differentiate between non-accidental injury and primary bone fragility conditions, and the two are not mutually exclusive.

Cervical spine pathology both traumatic and non-traumatic is recognised; traumatic injuries, particularly C2 pars fractures generally have a good neurological outcome; children with OI Type 11 and/or a Bruck phenotype (*FKBP10* or *PLOD2* gene variants) appear predisposed to abnormal cervical spine morphology with potential abnormal neurology, such that early and ongoing screening with designated cervical spine imaging is recommended.

In the peripheral nervous system, patients with *SPARC* gene variants may present with significant neuromuscular weakness and myopathic EMG mimicking a primary neuromuscular condition; small fibre peripheral neuropathies have been identified in 2 siblings with *P3H1* gene variants (Type 8 OI).

Children with rare, recessive types of OI, usually presenting with severe disease may have specific neurological features, for example, congenital ptosis and abnormal movement patterns in *WNT1*-related OI (Type 15).

Genotype-phenotype correlation and detailed clinical description is key to understanding the spectrum of discriminatory neurological features in OI, including the impact both primary and secondary on neurodevelopment, global and pervasive, and to be aware of possible dual pathology.

A systematic clinical approach to the neurological aspects of OI from a paediatric perspective will be presented.

IS23

Murine models for OI: Three decades and counting

Joan Marini

NICHD, NIH, Bethesda MD, USA

ABSTRACT

There was great excitement when Jaenisch presented his *mov13* mouse at an IntOI Meeting in Pavia around 1990. That transgenic mouse had a viral insertion in the first intron of *Col1a1*, blocking transcription of the affected allele, and confirming that disrupting the synthesis of a type I collagen alpha chain caused OI. Now there are over 20 murine models of various genes causing OI. Most were made by standard knock-in recombinant technology, although minigene technology and CRISPR are coming into usage. *Brtl*, the first OI model made with cre-lox technology, has a glycine substitution in one *Col1a1* allele, and was soon followed by the mouse modelling an Amish founder mutation in *Col1a2*. These and several other models with collagen structural defects provided bone tissue for investigations and, at times, led the field in surprising

directions. The expansion of genetic types of OI began with defects in procollagen proline 3-hydroxylation; a critical component of identifying the defective complex was the Crtap-null mouse. Some murine models have preceded the identification of the defective gene as causative for OI, such as the PEDF-null mouse or the Oasis-null mouse and were originally developed for other areas of investigation.

In the course of this presentation, we will

1. Review the available murine models for OI;
2. Highlight some major skeletal and non-skeletal insights from studies of these mice;
3. Review murine models as targets for developing therapeutics.
4. Put new models into context, including a mouse with a dominantly inherited type I procollagen C-propeptide cleavage defect, or a mouse with an Ifitm5 p.S42L substitution.

IS24

What can zebrafish tell us about osteogenesis imperfecta?

Paul Coucke

Center for Medical Genetics, Department of Biomolecular Medicine, Ghent University, Ghent, Belgium

ABSTRACT

In order to investigate skeletal development as well as for the development of new therapeutic approaches, animal models are required. Transgenic mice have been widely used for mimicking human skeletal diseases since this species share a high percentage of coding DNA (~85%) with humans and bone development and the skeletal elements are highly conserved between these two mammalian species. As in humans, bone remodeling takes place in the cancellous bone.

However, since generating and handling transgenic mice is expensive and time consuming, zebrafish (*DanioRerio*) has recently emerged as a model for studying skeletal disorders because of its short development time, genetic similarity to humans, small size, and low husbandry costs. Approximately 71% of protein-coding genes in the human genome have an ortholog in zebrafish. Every week zebrafish produces hundreds of eggs, which are externally fertilized, thus allowing fast and easy genetic manipulation. Moreover, zebrafish larvae are transparent, and they can be stained in whole-mount to study skeletal development and cartilage/bone mineralization. In addition, transgenic lines expressing fluorescent proteins under bone cell- or pathway- specific promoters enable in vivo imaging of differentiation and signaling at cellular level.

As in humans, bone development in zebrafish occurs by both intramembranous and endochondral ossification and several key genes playing a role in skeletogenesis are conserved across the two species. Despite the fact that there are also dissimilarities between human and zebrafish skeletogenesis (e.g. in zebrafish bone is not vascularized and the growth plate develops differently), several zebrafish models mimicking human OI have been generated and characterized in the last decade.

The different OI ZF models described so far, together with different approaches used to study the skeleton, published as well as unpublished, will be presented during the presentation.

IS25

Disease in a dish: modelling skeletal dysplasias using human induced pluripotent stem cells

Shireen Lamande^{1,2}, Elizabeth Ng¹, Trevor Cameron¹, Louise Kung¹, Lisa Sampurno¹, Lynn Rowley¹, Jinia Lilianty^{1,2}, Yudha Nur Patria^{1,2}, Tayla Stenta¹, Eric Hanssen², Katrina Bell¹, Kathryn Stok², Edouard Stanley^{1,2,3}, Andrew Elefanty^{1,2,3}, John Bateman^{1,2}

¹Murdoch Children's Research Institute, Parkville, Australia. ²University of Melbourne, Parkville, Australia. ³Monash University, Clayton, Australia

ABSTRACT

Although many genes and mutations underlying genetic skeletal disorders have been defined, our knowledge about the cellular and

extracellular pathological mechanisms is incomplete and is likely to be disease and mutation specific. A powerful emerging approach is differentiating induced pluripotent stem cells (iPSCs) into chondrocytes to produce in vitro cartilage, or into osteoblasts to model bone disease. This innovative "disease in a dish" approach is driven by the importance of studying patient-specific mutations in the context of the affected human skeletal tissues. We have developed and optimised iPSC differentiation protocols to model cartilage development and chondrocyte maturation to hypertrophy and then induce the hypertrophic chondrocytes to transdifferentiate to osteoblasts in 3D organoid culture – thus recapitulating endochondral ossification in vitro for the first time. Using genome editing we have produced iPSC lines with patient mutations in COL1A1, COL2A1 COL10A1 and TRPV4 (and isogenic controls) and are using our in vitro differentiation protocols to model skeletal disorders, define mutation specific pathogenic pathways and, ultimately, test candidate drugs. We can study the critical stages of skeletal development that are affected by mutations and our RNAseq and protein analyses are revealing mutation specific effects on the cells and tissues.

IS26

Early phase studies in OI

Brendan Lee

Baylor College of Medicine, Houston, USA

ABSTRACT

The development and regulatory approval of pharmacological therapies for OI has been hindered by locus and allelic heterogeneity leading to difficult to power clinical endpoints. At the same time the evolutionary conservation of the structural functions of the mouse and human skeleton has facilitated the development of mechanistically targeted treatments and dose finding. By establishing multi-center studies such as the NIH Brittle Bone Disorders Consortium, we are able to develop and power clinical endpoints that are stratified in clinical populations that reduce heterogeneity. Ultimately, the development of new clinical endpoints for example targeting quality of life measures as well as validated actigraphy may enable better powered clinical efficacy studies.

IS27

Clinical management of rare bone diseases: lessons and synergies across diseases

Outi Mäkitie

University of Helsinki, Helsinki, Finland. Karolinska Institutet, Stockholm, Sweden

ABSTRACT

Rare bone diseases encompass a large spectrum of disorders of bone strength, bone growth, or bone structure. Most of the disorders are caused by genetic defects and have their onset prenatally or in childhood. The International classification of genetic skeletal disorders includes >460 disorders divided into 42 subgroups based on their clinical, radiographic, and genetic features. The individual disorders are rare but collectively result in significant morbidity and pose a challenge to the health care system. Underlying pathology remains inadequately understood in most of these disorders and optimal targeted therapy is rarely available. Regardless of the specific diagnosis, some challenges are common to all patients with a rare bone disease. These may be related to for example 1) rarity of the disease, meaning that medical expertise is seldom available close to the patient and peer support from other affected individuals is difficult to find; 2) genetic nature of the disease, implying that genetic counselling to the parents and later to the affected individual is important; 3) complex diagnose-specific and age-dependent disease manifestations, requiring often life-long follow-up and management by a multidisciplinary team. The patient care should be centralized to expert centers with sufficient capacity and expertise to deal with both skeletal and extra-skeletal disease manifestations. Further multifaceted clinical and translational research is needed to enable

development of disease-specific management guidelines and novel therapies.

IS28

Integrated care: the holistic approach

Paul Arundel

*Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom.
University of Sheffield, Sheffield, United Kingdom*

ABSTRACT

Integration of care for those with rare bone diseases is desirable. When done well there are the benefits to individuals and families of timely, high quality care provided by accessible and durable services. But this is not always possible. Even when aims are shared between partners in the endeavour of integration, if the structures around them are not right then there will be failures. Failures incur various costs. Steps taken at the individual, team, organisational, and supra-organisational levels can all mitigate against these failures. From the perspective of a clinician facing both the day-to-day and strategic challenges of making integrated care work, I will provide a critical and hopeful view on how we work together to provide holistic care for a range of people affected by altered bone physiology.

IS29

Surgical solutions in abnormal bone conditions

Peter Smith

Shriners Children's Chicago, Chicago, USA. Orthopaedic Research Engineering Center, Milwaukee, USA

ABSTRACT

Bone has a remarkable ability to heal and remodel, adapting to the forces it sees, and this is true even in situations such as OI where a genetic defect causes an abnormality of collagen quality or quantity. However, frequent fractures over time, as well as deformities impossible to remodel and frequent immobilization lead to failure which can only be helped by surgical intervention.

Early work in the 1940s at the Shriners Hospital in Chicago established that fragmentation and rodding of the long bones in Osteogenesis Imperfecta is remarkably well tolerated and can lead to improved function. Since then modifications to the technique with advancements in imaging have improved rod longevity as well as hastened recovery.

Our understanding of the benefits and limitations of rodding, particularly as they relate to mobility and quality of life measures, has been informed by recent multicenter studies. Common errors can be avoided with experience in operating on brittle bone, such as instances where plates or bulky instrumentation can lead to stress shielding and junctional fractures.

The ultimate decision about the need and type of surgery, however, is unique to each individual, because of the extreme variability of the OI phenotype. We still don't know for each individual what the proper stiffness and strength of the instrumentation ought to be. Perhaps an understanding of material properties of OI bone could inform these decisions. Investigations over the past twenty-five years in our lab and others on the properties of OI bone and the use of finite element modeling to predict fractures have highlighted differences in stiffness, porosity and toughness from normal bone. Fortunately, the expanding variety of orthopaedic instrumentation and bone grafting materials allows for a more personalized approach to surgery than in the past.

Maximizing the longevity and effectiveness of our surgery demands sharing our results among colleagues and the wider orthopaedic community, so that more doctors can understand these rare bone challenges.

IS30

Surgical management of skeletal dysplasia – lessons for osteogenesis imperfecta

Tae-Joon Cho

Seoul National University Children's Hospital, Seoul, Korea, Republic of

ABSTRACT

Orthopaedic surgeons have developed various surgical options for the management of skeletal dysplasia (SD) patients. This talk will not cover the management of spine, but will focus on the limb problems. Most SDs manifest short stature, limb deformity, joint malformation and/or subsequent joint destruction. Osteogenesis imperfecta (OI) patients share some of these manifestations, however the pathomechanism is not the same. Hence, the surgical options should not be the same.

In SD patients, the limb deformity usually develops from abnormal growth at the physis, thus is located at the metaphysis. In contrast, in OI patients, it develops from frequent fractures and malunion, thus it is diffuse or multifocal, and is usually located at the diaphysis. In SD patients accurate correction of the deformity and restoration of the alignment are important, while in OI patients straightening and augmenting the strength of the limb segment are important. SD patients have more diverse options for limb deformity correction including acute or gradual correction fixed with plate and screws, IM rod, tension band wiring, and external fixator. On the other hand, in OI patients, rigid IM rod is widely used and only rarely plate and screws or external fixator are indicated. Guided growth technique is a very useful in the angular deformity correction in growing children with SD, but osteopenia in OI patients limit its use. Distraction osteogenesis using external fixator is a strong armament for the limb deformity correction in SD. However, its use is very limited in OI, because the osteopenic host bone does not tolerate prolonged application of external fixator. Moreover, limb lengthening by distraction osteogenesis impose too much stress to the joint, and runs a risk of joint deformation in OI patients. Because limb lengthening surgery is not well indicated in OI, and epiphysiodesis outcome is not predictable, leg length equalization is challenging in OI. Joint preserving surgery or joint replacement surgery is also very difficult and highly likely to produce severe complications in OI patients. In general, the surgical plan and option for OI patients should be different from those for SD patients, and are usually more challenging.

IS31

Intramedullary nailing in OI. Challenges and opportunities

Paul Esposito

University Nebraska Medical Center, Omaha, USA. Children's Hospital and Medical Center, Omaha, USA

ABSTRACT

Intramedullary rodding in conjunction with bisphosphonate treatment has improved the quality of life for many patients with OI. Early intramedullary rodding and realignment for severe deformity has allowed enhanced psychomotor development in young children but also requires frequent revisions because of the short rods, and variable telescoping. Limiting immobilization has also been important in avoiding worsening osteoporosis, joint stiffness, and muscular weakness.

Rotational control in telescoping devices is also lacking in present systems, and although there are locking intramedullary devices with smaller diameter for individuals who are skeletally mature there are still individuals who are too small for these devices, and the devices themselves are not always easy to use.

Nonunion following correction of severe deformity is still an issue, and although the incidence does not appear to be any different than it was prior to bisphosphonate treatment, this continues to be a vexing issue. Utilizing fixation to control rotation, and stability in conjunction with an intramedullary nail has been highly effective along with grafting.

Whether or not the plates need removed remains unclear and obviously any opportunity to avoid surgery in this patient population is important.

Indications for upper extremity surgery are still being defined, but it is clearly, if the child cannot sit up because of recurrent fractures and deformity, that stabilization and realignment should be considered. There is growing evidence, then individuals who sustained significant bowing of the ulna, but not radius are also prone to dislocating the radial heads over time and prophylactic realignment and stabilization with intramedullary nails may prevent this. At present time, there are no telescoping nails appropriate for the forearm, and although the Slim nail can be used the threaded portion is relatively large.

Refining indications and developing newer devices may improve the quality of life of our patients even further.

IS32

Current and future treatment perspectives for osteogenesis imperfecta

Nick Bishop

Sheffield, Sheffield, United Kingdom

ABSTRACT

Current treatment for osteogenesis imperfecta is based on a multidisciplinary approach, with medical therapeutic interventions largely using bisphosphonates. Despite their widespread use, the evidence for anti-fracture efficacy is limited and largely demonstrated only in more mildly affected children using oral interventions. Emergent therapies have primarily focused on increasing bone mass, similar to approaches taken for adults with osteoporosis. Such treatments include both bone anabolic and catabolic agents, and some with both modes of action. In addition, new approaches targeting inflammatory components are also showing some promise. However, there is increasing awareness of the non-bone effects of the condition, in particular in regard to effects on muscles, the cardiorespiratory system and the brain, and as yet no specific therapies have been developed that address these areas.

Children and adults with osteogenesis imperfecta have differing views regarding their priorities for research into the condition, in particular the specific outcomes of interest, and their willingness to participate in placebo-controlled trials. In developing current and future treatment paradigms, an holistic approach incorporating consideration of the multisystem nature of the condition, and the views and interests of our patients, is needed.

OC1

Bispecific antibody neutralizing both sclerostin and Dickkopf 1 prevents fragility fractures and increases fracture healing rate in an osteogenesis imperfecta mouse model

Baozhi Yuan¹, Xiaofeng Liu¹, Kunfeng Liu¹, Huichun Xiao¹, Qingqiang Zeng¹, Hao Wang¹, Ann Zovein², Muyu Li¹, Ren Xu³, Xinluan Wang⁴, Hua Zhu Ke¹

¹Angitia Biopharmaceuticals, Guangzhou, Guangdong, China. ²Angitia Biopharmaceuticals, Boston, MA, USA. ³Xiamen University, Xiamen, Fujian, China. ⁴Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, Guangdong, China

ABSTRACT

Patients with osteogenesis imperfecta (OI) suffer from skeletal fragility, recurrent fractures, and complex bone deformities. Prior studies show that activating the Wnt pathway via antibodies against the Wnt inhibitor sclerostin (Scl-Ab) improved bone mass and bone strength in *oim/oim* mice, a model of severe OI. However, Treatment with Scl-Ab induced a compensatory increase in Dickkopf 1 (DKK1), another endogenous Wnt inhibitor that limits osteogenesis as well as fracture healing. In addition, elevated sclerostin and DKK1 levels were reported in patients with OI, which adversely affects their bone metabolism, bone mass and strength. We hypothesize that neutralizing both sclerostin and DKK1 may have additive or synergistic effects in increasing bone mass and reducing fracture incidence in *oim/oim* mice. Groups of *oim/oim* mice (n = 8-9) were treated twice-weekly (SC) from 4 to 10 weeks of age with either a bispecific antibody that neutralizes both sclerostin and DKK1 (Ab5, 25 mg/kg), Scl-Ab monotherapy (25 mg/kg), DKK1-Ab monotherapy (DKK1-Ab, 25 mg/kg), combination therapy with Scl-Ab and DKK1-Ab (25 mg/kg of each Ab), or vehicle (Veh). Ab5 reduced the average fragility fracture number per animal at 10 weeks of age, from 3.67 in PBS controls to 0.67 with Ab5 treatment, an 81.7% reduction. Ab5 also increased fracture healing rate through 10 weeks of age, from 40% with PBS to 86% with Ab5. μ CT analysis of the distal femoral metaphysis indicated significantly greater trabecular bone mineral density (BMD) with Ab5 vs all other groups. The Ab5 and combination groups also exhibited greater cortical bone mineral content (BMC) in the femoral mid-shaft vs Veh. Destructive 3-point bending tests of the femoral diaphysis revealed greater force after Ab5 vs Veh treatment, and greater stiffness after Ab5 vs Veh or monotherapy groups. The overall results from this study indicate that dual inhibition of sclerostin and DKK1 prevents fragility fractures and promotes fracture healing in *oim/oim* mice, with favorable effects on trabecular and cortical bone mass, density, and architecture that generally exceeded the effects of Scl-Ab or DKK1-Ab monotherapy.

OC2

Molecular mechanisms of lung pathology in a G610C mouse model

Elena Makareeva¹, Satoru Otsuru², Sergey Leikin¹

¹National Institutes of Health, NICHD, Bethesda, USA. ²University of Maryland School of Medicine, Baltimore, USA

ABSTRACT

OBJECTIVES: Pulmonary failure is the leading cause of death in OI. Mounting evidence suggests that lung function in OI is affected by both skeletal defects and intrinsic lung tissue pathology, e.g. alveolar disruption has been reported in mouse models and bronchial wall thickening in humans. The present study aims to provide mechanistic insights into the causes of the lung-intrinsic pathology in a G610C mouse model of moderate OI.

METHODS: Using histology, electron microscopy (EM), single-cell RNA sequencing (scRNASeq), fluorescent *in situ* mRNA hybridization (*FISH*), micro-CT, and plethysmography we examined wild type (WT), heterozygous (Het), and homozygous (Hom) E18.5 embryos as well as 3-, 5-, and 10-week-old WT and Het mice.

RESULTS: Hom G610C pups died at birth from lung failure caused by poorly developed saccular structures and massive parenchymal bleeding. In Hom E18.5 embryos, bone pathology was comparable to severely affected yet surviving Het animals while the lung pathology was more dramatic. In contrast to findings in osteoblasts, EM of lung fibroblasts revealed no ER disruption by mutant collagen and scRNASeq revealed no integrated stress response (expected to be caused by the ER disruption). EM, histology, and *FISH* revealed deficient extracellular matrix (ECM) deposition and disorganization of lung epithelial cells, which filled the developing lung saccules instead of lining them. Altered gene expression by epithelial, endothelial, and stromal lung cells suggested abnormal cell interactions with the deficient ECM. In Het embryos, the lung pathology was less severe. In 3- and 5-week-old Het mice, we observed alveolar disruption, reduced alveolar surface/volume ratio, and increased respiratory frequency and volume/minute at rest (apparently compensating for the alveolar surface loss). In addition, many 3- and 5-week-old Het mice had lesions with inflammatory cell infiltration and various degrees of fibrosis, probably resulting from weak ECM being prone to injury. In 10-week-old Het mice, the alveolar disruption, lesions, and respiratory abnormalities were less pronounced, likely because of lung remodeling.

CONCLUSION: Disruption of rapidly forming ECM and cell-ECM interactions in embryos and young animals by secreted mutant collagen molecules is the primary cause of the lung-intrinsic pathology in G610C mice.

OC3

Non-invasive quantification of bone remodeling dynamics in adults with OI using time-lapse high-resolution peripheral quantitative computed tomography imaging

Seyedmahdi Hosseinitabatabaei^{1,2,3}, Isabela Vitenes^{1,2,3}, Maximilian Rummler^{1,3}, Annette Birkhold⁴, Frank Rauch¹, Bettina Willie^{1,2,3}

¹Research Centre, Shriners Hospital for Children-Canada, Montreal, Canada.

²Department of Biomedical Engineering, McGill University, Montreal, Canada.

³Department of Pediatric Surgery, McGill University, Montreal, Canada.

⁴Siemens Healthineers GmbH, Erlangen, Germany

ABSTRACT

OBJECTIVES: Time-lapse imaging using high-resolution peripheral quantitative computed tomography (HR-pQCT; XCT-I & II) has emerged as a novel method to quantify dynamic bone (re)modeling. However, there is no consensus on how to perform the procedure. Using repeated scans from adults with osteogenesis imperfecta (OI), we examined the influence of various parameters on HR-pQCT-derived bone formation and resorption to identify the optimal methodology.

METHODS: At 10 sites within a multi-center trial of the ASTEROID study, the radii and tibiae of 29 participants (19-65yrs, OI-type: I,IV) were scanned twice on the same day with full repositioning. In repeated scans without motion (n=13), bone (re)modeling indicate error. Thus, we evaluated several parameters to minimize (re)modeling. We aligned the scans and performed time-lapse morphometry while altering the input image (binary [i.e., voxel is bone or zero] or grayscale [i.e., voxel value corresponds to bone density]), registration method (3D [i.e., rotate one image toward the other image] or matched-angle [MA; rotate both images halfway toward each other]), and segmentation mask (same or different periosteal mask). Additionally for grayscale images, different values for the density difference between voxels to be considered formed or resorbed, the minimum size of formation/resorption clusters, and gaussian smoothing sigma were evaluated.

RESULTS: For XCTI, the binary method yielded formed/resorbed volumes of 15% and 12% for the 3D- and MA-registrations, respectively. For XCTII, the 3D- and MA-registered formed/resorbed volumes were ~8%. For the grayscale method, the 3D and MA-registrations were similar. Using the same periosteal mask was preferred since different masks resulted in erroneous periosteal formation/resorption. For XCTI, a density threshold of 200 mgHA/cm³, a cluster size of 0, and gaussian sigma of 0.8 were optimal. For XCTII,

the optimal parameters were 200, 0, and 1.2. These settings had formation/resorption volumes approaching zero, negligible effect of increasing the density threshold and cluster size, and negligible noise (speckles of formation/resorption).

CONCLUSIONS: Our analyses indicated that 3D or MA-registered grayscale images, using the same mask, and gaussian smoothing are preferable for time-lapse HR-pQCT as a non-invasive clinical tool to assess (re)modeling.

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OC4

Fracture-targeted anabolics for treatment of osteogenesis imperfecta fractures

Stewart Low¹, Jeffery Nielsen¹, Xinlan Lu¹, Arden Shen², Mini Thomas¹, **Karen Smith¹**

¹Quince Therapeutics Inc, West Lafayette, USA.

²Purdue University, West Lafayette, USA

ABSTRACT

OBJECTIVES: We have developed a systemically administered fracture-targeted therapeutic with a high affinity to bone fractures. The compound can be administered in a distal spot from the fracture but accumulates locally at the fracture site. By improving the specificity of anabolics to fractures, we see significantly accelerated bone repair, reduced systemic affects, and no ectopic bone formation. We have previously demonstrated excellent fracture healing compared to saline, teriparatide, and abaloparatide in healthy, osteoporotic, and diabetic mice. Here we explore efficacy in fractures induced in the OI mouse model Colla2oim.

METHODS: Our fracture-targeted bone anabolic agent was prepared by synthesizing an abaloparatide-like peptide conjugated to a hydroxyapatite-homing acidic oligopeptide (named Ab46-D-Glu20). *in vivo* experiments were conducted in heterozygous and homozygous Colla2oim mice of both genders. Breeding pairs were composed of a homozygous male with two heterozygous females. Stabilized fractures were induced in 12-week old mice by inserting a locking nail in the right femur and inducing fractures with an Einhorn 3-point bending device. Mice were dosed with 38 nmol/kg/d of Ab46-D-Glu20 or saline. Following a 4-week study in heterozygous mice and 6-week in homozygous mice, fracture callus densities were measured using microCT (Scanco).

RESULTS SECTION: A marked increase in bone volume fraction of 50-55% was observed in both homozygous and heterozygous Ab46-D-Glu20 groups over their respective saline groups ($p < 0.05$). Moreover, mechanical testing yielded between 240% increase in force to fracture in the Ab46-D-Glu20 over the saline control groups ($p < 0.05$). Similarly, work to fracture assessments showed in a 60% increased trend in the Ab46-D-Glu20 over the saline control (+/-).

CONCLUSION: OI patients are an underserved population that would greatly benefit from a treatment that, in conjunction with conventional therapy, not only improves fracture repair but is safe enough to use periodically throughout a patient's lifetime. By targeting bone anabolic agents to bone fractures, we can deliver sufficient concentrations of anabolic agent to the fracture site to safely accelerate healing.

OC5

The IMPACT survey has produced a self-reported, 2,276-respondent dataset of individuals with OI, their caregivers and close relatives

Frank Rauch¹, Michael B Bober², Cathleen Raggio³, Lena Lande Wekre⁴, Ingunn Westerheim⁵, Taco van Welzenis⁵, Tracy Hart⁶, Maria Rapoport⁷, Samantha Prince⁷, Oliver Semler⁸

¹McGill University, Montreal, Canada. ²Alfred I. duPont Hospital, Wilmington, USA.

³Hospital for Special Surgery, New York, USA. ⁴TRS National Resource Center for Rare Disorders, Sunnaas Rehabilitation Hospital, Bjørnemyr, Norway.

⁵Osteogenesis Imperfecta Federation Europe, Heffen, Belgium. ⁶Osteogenesis Imperfecta Foundation, Gaithersburg, USA. ⁷Wickenstones Ltd, Abingdon, United Kingdom. ⁸University of Cologne, Cologne, Germany

ABSTRACT

OBJECTIVES: To date, few datasets comprehensively describe the experience and quality of life of individuals with osteogenesis imperfecta (OI). A better understanding of the real impact of OI on individuals, their caregivers and families, and wider society is needed to support future OI treatment and care and the rights of the OI community.

METHODS: In collaboration with the OI Federation Europe and OI Foundation, we have developed an international survey in eight languages. The survey was fielded using an online platform (fielding period July-September 2021) and aimed at adults with OI (≥ 18 years of age), adolescents with OI ($\geq 12-17$ years of age), caregivers (with or without OI) of children (≤ 18 years of age), or adults with OI and close relatives of individuals with OI. This survey focussed on the patient healthcare journey, worries and concerns, impact on individuals and their families, and the financial impact of OI. Non-English language responses were translated into English. All data were cleaned, coded, validated and analysed using StataSE 17.0.

RESULTS: Overall, 2,276 individuals participated in the surveys: 1,291 adults with OI, 712 caregivers of children or adults ($n=62$) with OI (of whom 148 were also diagnosed with the condition), 95 adolescents with OI and 116 close relatives responded to the survey. Caregivers provided proxy data on 787 children with OI. Most respondents lived in Europe ($n=1,559$) and North America ($n=499$); fewer respondents from South America ($n=119$), Asia ($n=71$), Australia ($n=53$) and Africa ($n=14$) participated. In this sample 66 countries were represented. Participants self-reported mild ($n=536$; 34.9%), moderate ($n=718$; 46.8%) or severe OI ($n=220$ 14.3%). Among caregivers and adults with OI, most respondents were female (81.3% and 70.3%, respectively). Among adolescents with OI similar proportions of male and female respondents were observed (52.3% female).

CONCLUSION: Our sample is the most comprehensive self-reported dataset of individuals with OI and proxy-reported data on children with OI. Further analysis will elucidate the experience of living with OI and enable a better understanding of the impact this condition has on individuals, their families and wider society.

OC6

TMEM38B-null OI osteoblasts have altered differentiation, mineralization, and cellular adhesion processes

Milena Jovanovic, Apratim Mitra, Ryan Dale, Joan Marini
NICHD/NIH, Bethesda, USA

ABSTRACT

OBJECTIVES: Osteogenesis Imperfecta (OI) is a heritable collagen-related bone dysplasia characterized by bone fragility and growth deficiency. Type XIV OI is a recessive form caused by null mutations in *TMEM38B*, encoding the ER membrane K⁺ channel TRIC-B, which alters intracellular Ca²⁺ flux. We previously showed that deletion of *TMEM38B* affects collagen synthesis. Here we investigate cultured *TMEM38B*-null osteoblasts to further understand how absence of TRIC-B contributes to OI type XIV pathophysiology.



METHODS: Osteoblasts differentiation, RNA-Seq, RT-qPCR, Western blot, immunocytochemistry, BrdU assay, electron microscopy of proband osteoblasts compared to age-matched control.

RESULTS: *TMEM38B*-null differentiated osteoblasts have decreased *COL1A1* and *SPARC* transcripts, but increased *ALPL*, *IBSP* and *DMP1*, associated with significantly delayed *in vitro* mineralization vs control. RNA-Seq transcriptomics of time-course differentiated osteoblasts showed cell adhesion is among the most significantly downregulated signaling pathways in *TMEM38B*-null osteoblasts vs. control. Twenty differentially expressed genes related to cell adhesion pathway, including cadherins, protocadherins, tight and gap junction, and genes with bone function were validated by RT-qPCR, confirming cell adhesion is affected in *TMEM38B*-null osteoblasts vs control. Tight and gap junction protein levels (ZO-1, Cx43) are downregulated in *TMEM38B*-null osteoblasts on Western blot and immunocytochemistry. Proliferation of *TMEM38B*-null osteoblasts was strongly reduced by BrdU assay, as was the proliferation marker Ki67 by immunocytochemistry. Multiple cyclins (D1, D3, D2, E1, B1) were reduced in *TMEM38B*-null osteoblasts on Western blot. Interestingly, CTGF, an extracellular matrix component secreted by osteoblasts and implicated in cell proliferation and cell-matrix adhesion via cell surface integrins, was downregulated in *TMEM38B*-null osteoblasts. HSP47, a collagen-specific chaperone, was increased at baseline but decreased later in differentiation, potentially affecting collagen folding or crosslinking. Electron microscopy of *TMEM38B*-null osteoblasts showed severely dilated ER and strikingly abnormal mitochondria, which were slim, and many-fold elongated with cristolysis, suggesting impaired cell energetics. After treatment with TGF β -1, *TMEM38B*-null osteoblasts had reduced p-SMAD3 and total SMAD3, suggesting TGF β signaling is altered.

CONCLUSION: Our results revealed novel roles of *TMEM38B* in regulation of bone homeostasis by impacting osteoblast proliferation, differentiation, and cellular adhesion. Mitochondrial abnormalities may be direct effect of abnormal Ca²⁺ flux or secondary effect of ER stress.

OC7

Conditional trimeric intracellular cation channel B knockout mouse: a tool to study osteogenesis imperfecta type XIV

Roberta Besio¹, Barbara Contento¹, Nadia Garibaldi¹, Marta Filibian¹, Stefan Sontag^{2,3}, Doron Shmerling³

¹University of Pavia, Pavia, Italy. ²LIMES-Institute, University of Bonn, Bonn, Germany. ³PolyGene AG, Rümlang, Switzerland

ABSTRACT

OBJECTIVES: The autosomal recessive osteogenesis imperfecta (OI) type XIV is caused by mutations in the *TMEM38B* gene encoding for the ER trimeric intracellular cation channel B (TRIC-B), a K⁺-specific channel necessary to regulate intracellular calcium flux. How mutations in this channel cause the disease is still puzzling the field. In order to address this question and to evaluate the TRIC-B function *in vivo* specifically in the bone tissue, we generated a *Tmem38b* osteoblast specific conditional knock-out mouse (*Runx2Cre;Tmem38b^{fl/fl}*).

METHODS: The Cre/loxP system was used to remove the exon 3 of the *Tmem38b* gene using mice expressing Cre recombinase under the early osteoblast specific *Runx2* promoter. The genomic targeting was confirmed by sequencing and the lack of TRIC-B by western blot. X-ray, micro computed tomography and skeletal staining were used for phenotype characterization. Primary calvarial osteoblasts were employed to evaluate the impact of loss of TRIC-B function on osteoblasts activity.

RESULTS: Mutant mice revealed grow delay and long bone deformities and fractures, in accordance with OI patients' phenotype. Importantly, over 80% lethality was detected within the first 38 days, indicating the impact of the bone fracture and deformation on the severity of the disease. Tibia 3D reconstruction by micro computed tomography revealed a smaller misshaped bone in the mutant. The analyses of both cortical and trabecular bone compartments showed a significative impairment in most of the geometrical properties in the

Runx2Cre;Tmem38b^{fl/fl} mouse, indicating the presence of an osteoporotic phenotype. Decreased mineralization and alkaline phosphatase activity, as well as a delay in cell differentiation, were found in the mutant following *in vitro* studies on primary osteoblasts.

CONCLUSION: The osteoporotic phenotype found in the *Runx2Cre;Tmem38b^{fl/fl}* mouse proves the primary function of osteoblast TRIC-B for bone development.

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OC8

Zebrafish *tmem38b* Knock out unveils the *in vivo* role of Trimeric Intracellular Cation (TRIC) channel B on cell homeostasis

Francesca Tonelli¹, Laura Leoni¹, Valentina Daponte¹, Cecilia Masiero¹, Roberta Gioia¹, Silvia Cotti², Daria Larionova², Imke A.K. Fiedler³, Bjorn Busse³, Eckhard Witten², Antonella Forlino¹

¹Department of Molecular Medicine, Biochemistry Unit, University of Pavia, Pavia, Italy. ²Department of Biology, Ghent University, Ghent, Belgium.

³Department of Osteology and Biomechanics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

ABSTRACT

OBJECTIVES: *TMEM38B* encodes the endoplasmic reticulum (ER) potassium channel TRIC-B, which indirectly modulates Ca²⁺ exit from the ER. Ca²⁺ is required for collagen type I assembly and as cofactor for enzymes responsible for collagen type I post-translational modifications. Mutations in *TMEM38B* cause recessive osteogenesis imperfecta (OI) type XIV, characterized by under-modified collagen type I and ER stress. Individuals affected by this OI form show a wide range of phenotypes whose molecular basis is still unknown. To better understand the link between TRIC-B activity and OI *tmem38b* mutant zebrafish were generated.

METHODS: *tmem38b* mutants were generated by CRISPR/Cas9. Alizarin red staining was performed to evaluate mineralization. MicroCT and nanoindentation were used to evaluate bone properties. Transmission electron microscopy was used to evaluate ER cisternae size. Collagen was analysed by SDS-PAGE. The expression of the collagen specific chaperone heat shock protein 47 (Hsp47) was determined by whole mount immunohistochemistry with or without 4-phenylbutyrate. Tail regeneration assay was employed to investigate bone modelling.

RESULTS: Two *tmem38b* zebrafish mutants were generated: one carrying a frameshift mutation resulting in a premature stop codon (*tmem38b^{-/-}*) and one with an in-frame deletion, which impairs Tric-b pore channel domain. *tmem38b^{-/-}* shows significant growth retardation at 21 dpf and 1 mpf linked to a reduced size of vertebral centra. Shape and mechanical properties remained normal. The enlarged ER cisternae size and the increased Hsp47 expression observed in both mutants suggest collagen type I retention in the ER, partially rescued by 4-phenylbutyrate. Defects in bone cells activity were evaluated in regenerated tails.

CONCLUSION: *tmem38b* mutants recapitulate the intracellular stress condition reported in OI type XIV patients' cells and knockout murine model, extending ER as potential target for pharmacological treatment also for OI type XIV.

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OC9

Mutations in SEC16B causes bone fragility and muscular hypotonia

Ahmed El-Gazzar¹, Barbara Voraberger¹, Frank Rauch^{2,3}, Mario Mairhofer⁴, Katy Schmidt⁵, Brecht Guillemyn⁶, Goran Mitulović^{7,8}, Robert Kopajtich⁹, Holger Prokisch^{9,10}, Susanne Kimeswenger¹¹, Oliver Drews¹², Vrinda Saraff¹³, Nick Shaw¹³, Nadja Fratzl-Zelman^{14,15}, Sofie Symoens⁶, Peter Byers^{16,17}, **Wolfgang Högl**¹

¹Department of Paediatrics and Adolescent Medicine, Johannes Kepler University Linz, Linz, Austria. ²Shriners Hospital for Children-Canada, Montreal, Canada. ³Department of Human Genetics, McGill University, Montreal, Canada. ⁴Department of Medical Engineering and Applied Social Sciences, University of Applied Sciences Upper Austria, Linz, Austria. ⁵Centre for Anatomy and Cell Biology, Medical University of Vienna, Vienna, Austria. ⁶Center for Medical Genetics, Department of Biomolecular Medicine, Ghent University, Ghent University Hospital, Ghent, Belgium. ⁷Clinical Department of Laboratory Medicine Proteomics Core Facility, Medical University Vienna, Vienna, Austria. ⁸current address Bruker Austria, Vienna, Austria. ⁹Institute of Neurogenomics, Helmholtz Zentrum München, Munich, Germany. ¹⁰Institute of Human Genetics, Technische Universität München, Munich, Germany. ¹¹Department of Dermatology, Johannes Kepler University Linz, Linz, Austria. ¹²Biomedical Mass Spectrometry, Center for Medical Research, Johannes Kepler University Linz, Linz, Austria. ¹³Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, United Kingdom. ¹⁴Ludwig Boltzmann Institute of Osteology at Hanusch Hospital of OEGK and AUA Trauma Centre Meidling. ¹⁵1st Medical Department Hanusch Hospital, Vienna, Austria. ¹⁶Vienna Bone and Growth Center, Vienna, Austria. ¹⁷Department of Laboratory Medicine and Pathology, University of Washington School of Medicine, Seattle, USA. ¹⁸Division of Medical Genetics, Department of Medicine, University of Washington School of Medicine, Seattle, USA

ABSTRACT

OBJECTIVE: Osteogenesis imperfecta (OI) is a genetically heterogeneous disorder characterized by frequent fractures, and growth delay. Using whole exome sequencing we identified a homozygous mutation in SEC16B in exon 4 (NM_033127.3: c.424C>T; p.Arg142Trp) in a ten-year-old boy of consanguineous background with clinical and radiological features of OI in whom targeted panel sequencing failed to identify a cause. The SEC16B protein is part of the endoplasmic reticulum (ER) transition zone and interacts with part of the COPII proteins to facilitate large protein secretion. We analyzed the bone ultrastructural phenotype and the functional effect of the SEC16B mutation in cultured fibroblasts to understand the disease mechanism.

METHODS: A transiliac bone biopsy sample was assessed by histomorphometry and quantitative backscattered electron microscopy. Expression of collagen type I was analyzed in patient and healthy fibroblasts, including in ER and Golgi subfractions by western blotting (WB) and immunofluorescence (IF). Mass spectrometry (MS) and proteomics were performed to detect alterations of type I collagen and cellular protein expression, respectively. Transmission electron microscopy (TEM) was performed to monitor autophagosome formation and markers of apoptosis and ER stress were measured by WB. Collagen secretion from the cells to the extracellular space was analyzed using the pulse chase experiment. Finally, gene editing was used to correct the single nucleotide mutation and to re-assess cellular function using IF and WB.

RESULTS: Bone analysis demonstrated reduced BV/TV (-45%), cortical width (-78%) and increased matrix mineralization, typical for OI. SEC16B mutant cells accumulated type I procollagen and SEC16B in the ER. Patient cells exhibited accelerated cellular collagen type I secretion, increased ER stress markers and enhanced autophagosome formation (7.6 fold change) and apoptosis (>8 fold change). Type I procollagen in mutant cells was differentially processed post-translationally. COPII machinery components SEC23/SEC24 and SEC13/SEC31 were reduced in patient cells. In genetically engineered patient cells transfected with wildtype SEC16B, type I procollagen no longer accumulated in the ER and autophagy normalized which confirmed the pathogenicity of the mutation.

CONCLUSION: The homozygous mutation in the novel disease gene SEC16B impairs COPII function and type I procollagen transport to

Golgi, increases ER stress and autophagosome biogenesis resulting in a bone and clinical phenotype of OI.

OC10

Homozygous *Kdelr2*-mutant mice display defects in endochondral and intramembranous bone formation

Alice Stephan¹, Julia Etich², Simon Tröder³, Mirko Rehberg¹, Branko Zevnik³, Anja Niehoff⁴, Oliver Semler¹, Frank Zaucke²

¹Department of Paediatrics, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. ²Dr. Rolf M. Schwiete Research Unit for Osteoarthritis, University Hospital Frankfurt, Frankfurt/Main, Germany. ³Cologne Excellence Cluster for Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany. ⁴Institute of Biomechanics and Orthopaedics, German Sport University Cologne, Cologne, Germany

ABSTRACT

OBJECTIVES: Recently, we identified *KDEL2* as novel osteogenesis imperfecta (OI)-causing gene that encodes the KDEL ER protein retention receptor 2 (KDEL2). This receptor shuttles ER-resident proteins from the Golgi back to the ER.

The disease mechanism of *KDEL2*-associated OI is still incompletely understood. Therefore, we generated a *Kdelr2* mouse model harboring a patient mutation to investigate the underlying mechanisms *in vivo*. In this study, we aim to analyze the bone and cartilage phenotype macroscopically and histologically.

METHODS: CRISPR/Cas gene editing was used to generate a mouse line harboring a C duplication resulting in c.448dupC that leads to a frameshift and premature stop codon in *Kdelr2*. Genotypes of the offspring were assessed by restriction fragment length polymorphism PCR and verified by Sanger sequencing to discriminate between wildtype (WT), heterozygous (HET) and homozygous mutants (HOM). The macroscopic phenotype was analyzed by whole mount stainings with Alizarin Red/Alcian Blue. Furthermore, Von Kossa/SafraninO and immunofluorescence stainings for collagen I (COL I) and IX (COL IX) were performed on tibial sections.

RESULTS: Mating of heterozygous animals reveals that genotype distribution deviates from Mendel's law (WT 31% HET 53% HOM 16%). HOM newborns die perinatally and display smaller stature (whole tibia length: WT 4.3 ± 0.03 mm HET 4.2 ± 0.04 mm HOM 3.7 ± 0.01 mm). Furthermore, HOM animals display clavicle malformations. In histological stainings, trabecular bone is reduced and less mineralized (COL I -43%, Von Kossa -58%). Additionally, hypertrophic chondrocytes appear to be larger.

CONCLUSION: This mouse model reveals that the *KDEL2* is important for both intramembranous and endochondral bone formation.

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OC11

The role of *KDEL2* in the bone-related mechanism of osteogenesis imperfecta

Lidiia Zhytnik^{1,2,3}, E Marelise W Eekhoff^{4,3}, Lisanne E Wisse^{1,3}, Nathalie Bravenboer^{5,3}, Gerard Pals^{1,3}, Alessandra Maugeri¹, **Dimitra Michal**^{1,3}

¹Department of Human Genetics, Amsterdam UMC, Amsterdam, Netherlands. ²Department of Traumatology and Orthopedics, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia. ³Amsterdam Movement Sciences, Amsterdam, Netherlands. ⁴Department of Internal Medicine, Section Endocrinology, Amsterdam, Netherlands. ⁵Department of Clinical Chemistry, Amsterdam UMC, Amsterdam, Netherlands

ABSTRACT

OBJECTIVES: We have previously discovered bi-allelic loss-of-function variants in *KDEL2* as a cause of severe osteogenesis imperfecta (OI). This gene codes for the KDEL endoplasmic reticulum (ER) retention

receptor 2 protein, which facilitates the COPI retrograde transport of ER-resident proteins with a KDEL-like motif from the cis-Golgi back to the ER. *FKBP10* and *SERPINH1* code for FKBP65 and HSP47 respectively; these are chaperone molecules with a KDEL-like motif, genetic defects in which also cause OI. Patients with KDEL2 defects, present reduced expression of FKBP65 and HSP47 and abnormal quality of secreted collagen fibrils in dermal fibroblasts. However, limited evidence exists about the pathogenic mechanism of KDEL2 leading to bone fragility and malformation. Our objective was to shed light on the mechanism of KDEL2 in OI bone pathology by investigating its role in primary human osteoblasts and mesenchymal stem cells (MSCs) as well as skeletal development of zebrafish after its knockdown.

METHODS: The expression of *kdelr2a* was knocked down in nacre zebrafish with splice- and translation-blocking morpholinos and skeletal malformations were examined 4-5 days post fertilization (dpf). *KDEL2* expression was knocked down with siRNA in osteoblasts treated with or without mineralization media, as well as MSCs and fibroblasts. The mRNA and protein expression of FKBP65 and HSP47 was investigated by qPCR and western blotting respectively.

RESULTS: Zebrafish showed with both morpholino types for *kdelr2a*, dose-dependent skeletal malformations at 4 dpf which included body axis curvature, frequently in combination with curled tail. On 5 dpf the viability of the severely malformed zebrafish was decreased. In human osteoblasts and fibroblasts, 7 day *KDEL2* knockdown resulted in decreased FKBP65 protein expression. The decrease was less pronounced in MSCs. After treatment of the osteoblasts with mineralization media for 14 days, HSP47 expression was decreased following *KDEL2* knockdown. No changes were observed in the mRNA expression of FKBP65 and HSP47 in the different human cell types.

CONCLUSION: Our studies demonstrate that lack of *KDEL2* expression, which is observed in OI patients with pathogenic variants, dysregulates the bone development and reduces FKBP65 and HSP47 expression in osteoblasts, in line with the reported disease mechanism in patient fibroblasts.

OC12

Effects of neuraxial anesthesia on postoperative pain scores in children with osteogenesis imperfecta

Nicholas Bohannon¹, Eric Van Der Zwaag¹, Linda Huynh², Kaitlyn Pellegrino^{3,4}, Marcellene Franzen^{3,4}, Paul Esposito^{5,6}, Maegen Wallace^{5,6}, Jessica Goeller^{3,4}

¹College of Medicine, University of Nebraska Medical Center, Omaha, USA. ²MD/PhD Scholars Program, University of Nebraska Medical Center, Omaha, USA. ³Division of Pediatric Anesthesiology, Children's Hospital & Medical Center, Omaha, USA. ⁴Department of Anesthesiology, University of Nebraska Medical Center, Omaha, USA. ⁵Division of Pediatric Orthopedic Surgery, Children's Hospital & Medical Center, Omaha, USA. ⁶Department of Orthopaedic Surgery, University of Nebraska Medical Center, Omaha, USA

ABSTRACT

OBJECTIVES: Children diagnosed with Osteogenesis Imperfecta (OI) often require many orthopedic procedures throughout life. Although neuraxial anesthesia is widely used for lower extremity (LE) operations, limited information on the use of neuraxial anesthesia (epidural or caudal) in OI patients is available, and the perceived risk of complications is believed to outweigh the benefits, leading providers to consider this technique contraindicated. To assess neuraxial analgesia's impact on post-operative pain control, this technique was compared to systemic analgesia alone in children with OI undergoing a LE surgery. The primary outcome measured was post-operative pain scores with a secondary factor being whether adverse events occurred related to neuraxial use.

METHODS: A retrospective chart review of pediatric patients with OI who underwent a lower extremity orthopedic operation from 2000 to 2020 was conducted at a single institution. The patient demographics, OI type, type of procedure and anesthesia, number and type of bones operated on, pain scores, and perioperative complications were recorded.

Cases were separated into 3 groups: epidural (EPI), caudal (CAU) or solely systemic (SYS). These groups were evaluated using an analysis of variance (ANOVA).

RESULTS: 611 cases were completed on 194 patients. 48.6% were male and 51.4% female. There were 34.9% EPI, 9.8% CAU, and 55.3% SYS. Pain scores for POD 0, SYS: mean=3.9, SD=2.8 and CAU: mean=2.9, SD=2.6 with a p value = 0.031. Pain scores for POD 1, SYS: mean=4.3, SD=2.6, CAU: mean=3.2, SD=2.9, and EPI: mean=3.5, SD=2.9, with a p value ≤ 0.001. Pain scores for POD 2, SYS: mean=3.5, SD=2.5 and CAU: mean=2.3, SD=2.3 with a p value = 0.020. Pain scores for POD 3, SYS: mean=3.2, SD=2.5 and EPI: mean=2.3, SD=2.5 with a p value = 0.004. No adverse outcomes (bleeding, spinal cord injury, or iatrogenic fracture) were identified.

CONCLUSION: Pediatric patients with OI who underwent a LE surgery with neuraxial anesthesia, displayed statistically significant differences in postoperative pain scores on POD 0-3 compared to solely systemic anesthesia. The use of neuraxial techniques improved pain control and may decrease exposure to opioid analgesics. In addition, adverse events such as epidural hematoma, spinal cord injury, and iatrogenic fracture were not reported in any of the cases spanning two decades.

OC13

The 'F-Words' in Osteogenesis Imperfecta: our favourite words for child and family centred care

Belinda Crowe, Anita Freeman, Roisin Curtin, Catherine DeVile
Osteogenesis Imperfecta Service, Great Ormond Street Hospital for Children
NHS Foundation Trust, London, United Kingdom

ABSTRACT

OBJECTIVES: The World Health Organization's International Classification of Functioning, Health and Disabilities (ICF) is a biopsychosocial health model focusing on six domains: Health Condition, Body Structure and Function, Environmental Factors, Personal Factors, Activity, and Participation. Despite this professionals often adopt a medical model when identifying intervention targets, rather than focusing on meaningful outcomes for children and families. In 2011 *CanChild* developed the 'F-words' – function, family, fitness, fun, friends, and future, mapped to ICF domains, as a tool to aid goal setting, personalise interventions and achieve child and family centred outcomes. We aimed to apply the 'F-words' to children and young people with osteogenesis imperfecta (OI).

METHODS: Children aged 6 years and over attending our multidisciplinary OI clinic were invited to complete the F-words Goal Sheet in the waiting area between March 2020 and March 2022, identifying goals in each domain. This was reviewed during the appointment, to aid discussion and goal setting with professionals. Following the consultation participants completed a feedback questionnaire.

RESULTS: 52 children (56% male, 44% female) aged 6-16 years (mean 11 years) completed the F-words Goal Sheet and feedback questionnaire. 75% had OI type I, 15% type IV, 2% type III and 8% atypical OI. 58% were on bisphosphonates. 87% children found it helpful to complete the F-words Goal Sheet and 61% talked more in the appointment compared to previously. 90% reported they would be happy to use this tool again in the future and 90% would recommend the 'F-words' to other children with OI. Children "felt more involved", "understood more" and "got more information" during the appointment which was "more personal". Health professionals also gained additional information which helped identify personalised goals and children requiring referral to the OI team psychologist.

CONCLUSION: The 'F-words' is a valuable tool in OI to identify goals which are meaningful. It acts as a useful screening tool to highlight children requiring psychological support. When using the 'F-words', communication in healthcare settings improves and children and families participate more actively. We promote application of this tool across the spectrum of OI and encourage its adoption in clinical practice, research, and advocacy.

OC14

Regional neuromuscular blocks and pain catheters for perioperative pain control in the setting of Osteogenesis Imperfecta extremity orthopaedic procedures

Jeanne Franzone, Kenneth Rogers, Manish Purohit, Robert Lang, Richard Kruse, Kesavan Sadacharam
Nemours Children's Health - Delaware, Wilmington, USA

ABSTRACT

OBJECTIVES: Perioperative pain control for osteogenesis imperfecta (OI) patients undergoing reconstructive upper and lower extremity procedures is an important aspect of care. Adjunctive options to general anesthesia (GA) may provide perioperative pain control. Neuraxial regional anesthesia has been reported in the setting of OI. A paucity of data is available regarding regional nerve blocks. Our objective is to report a series of regional nerve blocks for OI patients undergoing reconstructive extremity procedures.

METHODS: This is a retrospective review of patients with OI undergoing extremity orthopedic procedures since 07/2018. Chart review was completed for demographics, OI type, procedures, type of block, opioid use and pain score (intraoperatively, 24 hours, 24-48 hours).

RESULTS: We identified 40 surgical encounters involving 29 patients (17 male, 42.5%). The average age was 9.7 years (3-26). The number of procedures per operative event was 1 (72.5%), 2 (17.5%) and 3 (10%). OI type 3 was most common (21, 52.5%). The average weight was 24.67 kg (9.8-47.3). The two most common procedures were equal in frequency at 10 each (25%) - humeral and femoral realignment and rodding. Twenty-five (62.5%) procedures were revisions. The type of blocks successfully performed included: Adductor canal, Axillary, Fascia-iliaca, Femoral, Interscalene, Lumbar plexus, Sciatic, Supraclavicular and Quadratus Lumborum. 92.5% included an indwelling catheter. Lumbar plexus was the most frequent lower extremity block (15/27, 55%). Supraclavicular catheter (6/13) was the most frequent upper extremity block. Intraoperative average fentanyl (mcg/kg) and morphine (mg/kg) were 3.76 (0-10.2) and 0.028 (0-0.32). PACU average Morphine (mg/kg) was 0.016 (0-0.10). PACU average pain score (scale 0-10) was 0.71 (0-3.6). Morphine, Dilaudid and Oxycodone use in the first 24 hours was 0.034, 0.0017, and 0.168 respectively. Average pain scores in the PACU and at 24 hours were 0.7 (SD = 1.2) and 1.7 (SD = 1.6) respectively. No adverse events related to the regional blocks were noted.

CONCLUSION: The use of regional nerve blocks with indwelling catheters was safe and effective in this series of OI patients undergoing extremity procedures as demonstrated by low pain scores and minimal perioperative use of opioids. Future work is underway to compare pain medication requirements to a control group of patients.

OC15

A novel 3D-bioprinted patient-specific bone organoid approach for studying mineral formation and mechanics of type XI osteogenesis imperfecta

Anke de Leeuw¹, Julia Griesbach¹, Tanja Minacci¹, Pei Jin Lim², Matthias Rüger³, Marianne Rohrbach², Cecilia Giunta², Marina Rubert¹, Ralph Müller¹

¹Institute for Biomechanics, ETH Zurich, Zurich, Switzerland. ²Connective Tissue Unit, Division of Metabolism and Children's Research Center, University Children's Hospital Zurich, Zurich, Switzerland. ³Department of Pediatric Orthopaedics and Traumatology, University Children's Hospital Zurich, Zurich, Switzerland

ABSTRACT

OBJECTIVES: While osteogenesis imperfecta (OI) has been extensively studied in mouse models and monolayer cultures, three-dimensional (3D) *in vitro* models, that more closely mimic the human bone microenvironment, may offer clinically relevant platforms to elucidate pathomechanisms and develop personalized treatments. Here, we

investigated bone formation and mechanics of 3D bioprinted type XI OI bone organoids using primary patient-specific osteoblasts.

METHODS: Osteoblasts were isolated from a 3-year-old female donor with type XI OI (*FKBP10* c.890_897dup (p.Gly300Ter)) and a metabolically healthy 15-year-old male. Cells were encapsulated in alginate-gelatin-graphene oxide hydrogels and extrusion 3D bioprinted as described previously [1]. Organoids were cultured in compression bioreactors for 8 weeks and subjected to uniaxial cyclic compressive loading (1% strain, 5Hz, 5 minutes, 5 times per week). Live/dead assays were performed to determine cell viability after bioprinting. The effect of *FKBP10* mutation on organoid tissue mineral density (TMD) and stiffness was investigated by weekly time-lapsed micro-computed tomography (micro-CT) and mechanical testing. Organoids were fixed and cryosectioned for histology, immunohistochemistry, and scanning electron microscopy to evaluate cellular phenotypes and mineralized matrix formation.

RESULTS: More than 90% of patient-derived cells survived the bioprinting process, with no significant differences between OI and healthy organoid groups. End-point compression testing revealed an average stiffness of 1.05 ± 0.30 N/mm for OI samples and 0.70 ± 0.48 N/mm for controls. Notably, a significantly higher average TMD of 149.38 ± 6.99 mg HA/cm³ was found in OI organoids compared to 138.17 ± 6.04 mg HA/cm³ in healthy controls after 56 days of culture ($p < 0.05$).

CONCLUSIONS: We successfully established a 3D *in vitro* patient-specific bone model for OI (type XI). From previous studies, we expected an increase in TMD to result in higher organoid stiffness [1]. However, when provided with the same extracellular matrix environment, OI osteoblasts were able to produce denser mineral than healthy controls with no significant difference in stiffness. Further investigation will be performed to elucidate the OI phenotype in bone organoids. The established bone organoid may become a powerful tool to study pathomechanisms for numerous OI mutations and facilitate the development and testing of advanced therapies on a patient-specific level.

References:

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OC16

Cell stress in hypertrophic chondrocytes is responsible for growth deficiency in G610C OI mice

Amanda Scheiber¹, Kevin Wilkinson¹, Akiko Suzuki¹, Motomi Enomoto-Iwamoto¹, Takashi Kaito², Kathryn Cheah³, Masahiro Iwamoto¹, Sergey Leikin⁴, Satoru Otsuru¹

¹University of Maryland School of Medicine, Baltimore, USA. ²Osaka University, Osaka, Japan. ³University of Hong Kong, Hong Kong, China. ⁴Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, USA

ABSTRACT

OBJECTIVES: Short stature is one of the major clinical features of osteogenesis imperfecta (OI). However, the mechanisms underlying growth deficiency in OI remain unknown and no effective treatment is available. Therefore, in this study, we sought to identify the mechanism of growth deficiency using G610C OI mice.

METHODS: To detect defects in the growth plate (GP) of G610C OI mice, we histologically evaluated the structure compared to wild-type mice. Chondrocyte proliferation and turnover in GP were examined by EdU incorporation assays. The fate mapping of hypertrophic chondrocytes (HCs) was performed using the Cre/loxP system in G610C OI mice. Specifically, we generated a novel quadruple strain from Col10a1-Cre knock-in mice, Ai9 reporter mice, Col1a1 2.3-GFP transgenic mice, and G610C OI mice. Triple strain without G610C OI mice served as non-OI control mice. In this model, HC descendants become red, mature osteoblasts/osteocytes become green, and HC-derived osteoblasts/osteocytes become yellow, allowing us to determine the number of HC descendants translocating to the trabecular area and becoming osteoblasts/osteocytes. The endoplasmic reticulum (ER) was

evaluated by electron microscopy. To confirm cell stress plays an important role, cell stress reducer, 4-phenyl butyric acid (4PBA), or PBS as control were administrated to mice. The effects of 4PBA were evaluated by μ CT, mechanical testing, and spatial transcriptomic analysis.

RESULTS: We found that G610C OI mice had the elongated GP and decreased cell turnover. G610C HCs had significantly dilated ER. Histological evaluation of the triple/quadruple strains demonstrated that both the translocation of HCs and the transition of HCs to osteoblasts were significantly suppressed in OI, suggesting that HCs stagnate in GP. 4PBA treatment improved the translocation and transition of HCs and significantly enhanced longitudinal bone growth. Moreover, 4PBA treatment corrected the upregulation of cell stress-related genes and reduced ER size in G610C HCs.

CONCLUSION: HCs were exposed to cell stress in G610C OI mice. Due to cell stress, HCs stagnated in GP. Reduction of cell stress in HCs with 4PBA successfully corrected these defects and enhanced linear bone growth. Therefore, cell stress in HCs is responsible for growth deficiency in G610C OI mice.

OC17

Collagen C-propeptide cleavage deficiency increases bone mineralization by increasing ossification pathways and decreasing collagen organization and mineral particle thickness

Aileen Barnes¹, M. Helen Rajpar¹, Joseph Perosky², Stéphane Blouin³, Basma Khoury², MaryAnn Weis⁴, Theresa Hefferan⁵, Ghazal Hedjazi³, David Eyre⁴, Peter Fratzl⁶, Kenneth Kozloff², Nadja Fratzl-Zelman³, Joan Marini¹

¹National Institutes of Health, Bethesda, USA. ²University of Michigan, Ann Arbor, USA. ³Ludwig Boltzmann Institute of Osteology, Vienna, Austria.

⁴University of Washington, Seattle, USA. ⁵Mayo Clinic, Rochester, USA. ⁶Max Planck Institute of Colloids and Interfaces, Potsdam, Germany

ABSTRACT

OBJECTIVES: Dominant mutations in the C-propeptide cleavage site of type I procollagen cause a distinct high bone mass (HBM) OI phenotype. We generated a heterozygous mouse model with an uncleavable COL1A1 C-propeptide to understand the role of C-propeptide cleavage in bone dysplasia.

METHODS: WT and HBM bones were examined by electron microscopy, mass spectrometry, mCT, mechanics, dynamic and static histomorphometry, qBEI for matrix mineralization and osteocyte lacunae, and SAXS for mineral particle analysis. Calvarial osteoblasts were used for mineralization and RNA-Seq of osteoblast differentiation.

RESULTS: Lack of full C-propeptide cleavage leads to pC-collagen and increased monomeric C-propeptide in bone tissue, causing a "barbed wire" appearance on EM. HBM bones have decreased collagen content, thin cortices and fewer trabeculae, but increased mature collagen crosslinks. Histomorphometry revealed increased osteoid volume, thickness, and surface, but decreased mineralizing surface. MAR and BFR/BS are normal, but mineralization lag time is increased. HBM femora are extremely brittle, with decreased stiffness, yield and fracture load, and severely decreased post-yield displacement on 4-point bending. qBEI revealed elevated CaMean, CaPeak and 4.7x increased CaHigh compared to WT, with CaPeak still increasing between 6- to 12-months, although WT levels had peaked. SAXS analysis showed that mineral particle thickness and degree of alignment are smaller in HBM. Unlike classical OI, HBM osteocyte lacunar density is decreased, but lacunar area is increased. The decreased osteocyte lacunar density may promote microcrack formation and increase bone remodeling, as reflected in increased serum TRAP and PINP levels. RNA-Seq gene ontology analysis of differentiated HBM osteoblasts showed that ossification was the top upregulated biological process at differentiation days 10, 15 and 21, with increased Alpl, Col1a1, Sp7, Bglap, Ibsp, Ifitm5 and Sost, confirmed by qPCR. Downregulated gene ontology pathways included extracellular matrix organization and structure, as well as decreased angiogenesis and vasculature pathways at days 15 and 21.

CONCLUSIONS: HBM mice have an extremely brittle, high mineralization phenotype. Mineralization increases with age, even after WT mineralization has peaked. A disorganized extracellular matrix with delayed ossification may lead to the incorporation of an increased number of small and disorganized mineral crystals, making bone more brittle than classical OI.

OC18

Evaluating the osteoanabolic potential of Galunisertib, a TGF- β receptor inhibitor, in mesenchymal stem cells isolated from Osteogenesis Imperfecta pediatric patients and in oim mice model

Arantza Infante¹, Natividad Alcorta-Sevillano¹, Iratxe Macías¹, Dalia Medhat², Ana M Bueno³, Belén Sagastizabal³, Maitane Arroyo^{4,1}, Maialen Stephens⁵, Javier Aldazabal⁶, Karen López-Linares⁵, Ainara Campino^{7,1}, Daniela Gerovska⁸, Marcos J Araúzo-Bravo⁸, Blanca Gener^{7,1}, Clara I Rodríguez¹

¹Biocruces Bizkaia Health Research Institute, Barakaldo, Spain. ²National Research Centre, Cairo, Egypt. ³Getafe University Hospital, Madrid, Spain.

⁴Basurto Hospital, Bilbao, Spain. ⁵Vicomtech Foundation, Donostia-San Sebastián, Spain. ⁶TECNUN - Universidad de Navarra, Donostia-San Sebastián, Spain. ⁷Cruces University Hospital, Barakaldo, Spain. ⁸Biodonostia Health Research Institute, Donostia-San Sebastián, Spain

ABSTRACT

OBJECTIVES: To study the *in vitro* and *in vivo* osteoanabolic effects of Galunisertib in OI-MSCs isolated from pediatric patients and in the oim mice model.

METHODS: MSCs were isolated from discarded and donated bone fragments from OI pediatric patients (mutations in either *COL1A1* or *COL1A2*) and age-matched healthy controls undergoing surgery. Primary cultures of OI-MSCs and CTRL-MSCs undergoing osteogenic differentiation were established and characterized by ALP (early differentiation) and ARS (late differentiation) staining. Gene expression (Q-PCR and RNAseq) and protein expression studies (western blot, in-cell western, immunofluorescence) were addressed to characterize the OI-MSCs and to evaluate the *in vitro* consequences of inhibiting TGF- β pathway with Galunisertib. Oim mice were treated with Galunisertib to study the *in vivo* effects of inhibiting the ALK5 receptor and trabecular bone microstructure and bone strength were studied (micro-CT and biomechanical tests).

RESULTS: The up-regulation of TGF- β pathway in OI-MSCs and its subsequent downregulation by Galunisertib treatment was confirmed in a subset of patients by evaluating the phosphorylation of Smad3. The expression and secretion of Collagen Type I, a known downstream target of TGF- β pathway, and the underlying molecular consequence of OI in the samples analyzed in this study, were found to be significantly downregulated in the presence of Galunisertib, in both MSCs and MSCs undergoing osteogenic differentiation. Consequently, Galunisertib treatment also ameliorated the secretion of the mutant Collagen Type I in OI-MSCs. The expression of BiP, a marker of the ER stress response, was downregulated after Galunisertib treatment. At the cellular level, Galunisertib treatment enhanced the osteoanabolic differentiation of OI-MSCs (increasing ALP expression and mineralization). Oim mice treated with 20 mg/kg of Galunisertib showed slight improvements in the bone microstructure although without impact on bone strength.

CONCLUSIONS: Our results suggest that the downregulation of global Collagen Type I expression elicited by Galunisertib could be ameliorating the ER stress response triggered by the mutant Collagen Type I proteins in OI. This lesser amount of Collagen Type I could have positive consequences on the osteoanabolic potential of OI-MSCs. We are currently assessing a higher dose of Galunisertib in addition to studying the underlying mechanism driving these improvements.

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OC19

Osteocyte Mechanoresponsiveness in Osteogenesis Imperfecta

Chen Zhang^{1,2}, Wouter H. Nijhuis³, Huib W. van Essen², Ralph J. Sakkars³, Jenneke Klein-Nulend¹, Nathalie Bravenboer²

¹Department of Oral Cell Biology, Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam and Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, Amsterdam, Netherlands. ²Department of Clinical Chemistry, Amsterdam University Medical Centers (UMC) location Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, Amsterdam, Netherlands. ³Department of Orthopaedic Surgery, University Medical Centre Utrecht, Wilhelmina Children's Hospital, Utrecht, Netherlands

ABSTRACT

OBJECTIVES: Osteogenesis imperfecta (OI)-patients with structural deficiency in type I collagen suffer from hypermineralized bone. Embedded in bone matrix are mechanosensitive osteocytes that orchestrate mechanical adaptation of bone. Osteocytes increase nitric oxide (NO) production and COX2 expression, but decrease SOST expression in response to mechanical loading, leading to changed osteoblast and/or osteoclast-activity. Osteocyte-mechanoresponsiveness depends on bone matrix characteristics^[1]. This study aimed to investigate whether OI-bone matrix abnormalities affect osteocyte-mechanoresponsiveness.

METHODS: Trabecular/cortical bone was retrieved from 7 OI-patients (age: 2-18, 5♂, 2♀) and 13 non-OI-patients (age: 2-18, 6♂, 7♀). Isolated trabecular bone osteocytes were cultured as monolayer, and treated by 1h pulsating fluid flow (PFF; 0.7±0.3 Pa, 5 Hz), either/not followed by 6 or 24h post-culture. NO-production was measured during PFF. Cortical bone explants (8.0×3.0×1.5mm) containing osteocytes were 5 min mechanically loaded (2000 or 8000 µε, 1 Hz), either/not followed by 6h post-culture^[2]. COX2 and SOST gene expression were quantified by RT-PCR at 6 and 24h post-culture.

RESULTS: PFF increased NO-production in monolayer OI-osteocytes by 2.7±1.7-fold (mean±SD) at 15 min, and 5.3±3.7-fold at 60 min. A similar trend was observed in monolayer non-OI-osteocytes (increase 2.1±0.7-fold at 15 min, 6.6±1.4-fold at 60 min). PFF did not affect COX2 expression in monolayer OI-osteocytes, but increased COX2 in monolayer non-OI-osteocytes by 2.9±1.1-fold immediately after PFF, and by 2.2±0.4-fold at 6h post-culture. Mechanical loading seemed to increase SOST expression in non-OI-bone explants by 2.1±1.4-fold at 2000 µε, and by 2.5±1.2-fold at 8000 µε at 6h post-culture. Mechanical loading seemed to decrease SOST expression in OI-bone explants by 0.4±0.33-fold at 2000 µε, but increased SOST by 1.6±0.8-fold at 8000 µε.

CONCLUSION: OI hypermineralized native bone matrix affects osteocyte-mechanoresponsiveness, suggesting that these osteocytes change the release of signaling molecules affecting bone adaptation, thereby causing bone fragility. This study might provide new insight in pathogenesis of OI, thus contributing to development of new strategies for OI treatment.

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OC20

Drug screening on OI human experimental models: increasing the osteoanabolic potential of MSCs

Natividad Alcorta-Sevillano^{1,2}, Arantza Infante¹, Iratxe Macias¹, Eider San Sebastian³, Javier Aldazabal⁴, Ana M Bueno⁵, Belén Sagastizabal⁵, Maitane Arroyo⁶, Ainara Campino^{1,7}, Blanca Gener⁷, Clara I Rodríguez¹

¹ISS Biocruces Bizkaia, Barakaldo, Spain. ²UPV/EHU, Leioa, Spain. ³UPV/EHU, Donostia, Spain. ⁴Tecnun - Universidad de Navarra, Donostia, Spain. ⁵Hospital de Getafe, Getafe, Spain. ⁶Hospital de Basurto, Bilbao, Spain. ⁷Hospital de Cruces, Barakaldo, Spain

ABSTRACT

OBJECTIVES: To develop new effective drugs for pediatric OI patients, based on the screening of potential osteoanabolic compounds for OI mesenchymal stem cells (MSCs).

METHODS: A drug library consisting of a total of 4480 compounds was *in vitro* screened to identify those exhibiting osteoanabolic effect; 3200 diverse and lead-like compounds, selected through computational chemistry to maximize the coverage of the chemical space plus over 1000 FDA-approved drugs. To this end, primary cultures of MSCs isolated from donated and discarded bone fragments of OI pediatric patients were characterized and differentiated into osteoblastic lineage. A first screening in 3 different OI-MSC lines treated with 2 concentrations of the compounds was performed, and those increasing alkaline phosphatase activity (ALP) (early differentiation marker) were selected. After the second screening, the absorption, distribution, metabolism, excretion and toxicity (ADMETox) profile of the new molecules was evaluated *in silico*, to discard those that may fail due to ADMETox problems. Preliminary *in vivo* studies were performed to analyze bone strength via biomechanical testing in oim mice intraperitoneally treated with 0,8 mg/kg of the selected osteoanabolic molecules, 3 times a week for 1 month.

RESULTS: During the first screening, 96 osteoanabolic compounds were selected and evaluated in a second screening. *In silico* predictions of ADMETox properties identified 4 potentially active compounds with similar profiles to those of approved drugs. In fact, these compounds presented the properties that an active principle ideally have: being effective all the time, easy to administer, cheap and without undesirable side effects. Finally, 1 of those 4 new molecules and 1 FDA-approved drug demonstrated preliminary promising outcomes *in vivo*: biomechanical parameters of female oim mice (n=3) treated with those molecules indicated improvement in bone strength. Currently we are conducting further studies to validate its efficacy *in vivo* and *in vitro*.

CONCLUSIONS: Our results points out the screening of osteoanabolic compounds based on OI MSCs as a relevant approach for developing new and effective drugs for OI.

FUNDING: ISCIII ("PI18/00202" and "PI21/0077"), co-funded by ERDF/ESF, "A way of making Europe"; Health Department, Basque Government (2021111073); Department of Education, under Predoctoral funding for non-doctoral Research Staff Training, Basque Country government (n° PRE_2021_2_0170).

OC21

The study between scoliosis and genotypes in Osteogenesis Imperfecta patients

YP Zhou¹, PK Chen^{1,2}, DY Lin¹, ZJ Tan^{1,3}, MKT To^{1,3}

¹Department of Orthopaedics and Traumatology, The University of Hong Kong-Shenzhen Hospital (HKU-SZH), Shenzhen, China. ²School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China. ³Department of Orthopaedics and Traumatology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

ABSTRACT

OBJECTIVES: To study the relations between scoliosis and genotypes in osteogenesis imperfecta (OI).

METHODS: We retrospectively studied 274 OI patients with genetic tests done 2015–2021 in our hospital. The patients' age, gender, genotype and scoliosis pattern and severity were evaluated. Scoliosis was defined as Cobb angle $> 10^\circ$ and progression was defined as $> 5^\circ$.

RESULTS: Within the 274 patients in our cohort, there were 107 patients (39.0%) had scoliosis (average age of 12.7 years). The mean follow-up was 5.3 years. Using an increment of 5° in Cobb angle as a marker of scoliosis progression, a total of 33 patients had scoliosis progression within our observation period. Of the 33 patients, 69% were male and 31% were female. COL1A1 and COL1A2 mutations account for 52%, WNT1 and FKBP10 mutations account for 9% each, with IFITM5 and P3H1 mutations account for 6% each when cross compare with genotypes. Using Sillence classification, type III Osteogenesis Imperfecta account for 70% of all the OI scoliosis patients. Our retrospective study shows that progression of scoliosis with an increase of 20 to 50° in curvature falls mainly between age 11 and 12.

CONCLUSIONS: OI patients are prone to develop scoliosis, with higher prevalence in Sillence type III patients. Patients with non type I collagen mutations are more likely to develop scoliosis. SERPINF1 and FKBP10 mutations tend to cause more severe scoliosis. The exact mechanism of both scoliosis and its progression in OI is complicated and has not been fully understood. Based on current studies, scoliosis is mainly influenced by OI severity, mutated OI related genes and age.

OC22

Pulmonary Function and Structure in Young Adults with Types III, IV and VI Osteogenesis Imperfecta

Bernadette Gochuico¹, Mahin Hossain¹, Sara Talvacchio¹, Mei Xing Zuo¹, Mark Barton¹, An Dang Do¹, **Joan Marin²**

¹National Institutes of Health, Bethesda, USA. ²National Institutes of Health, Bethesda, USA

ABSTRACT

OBJECTIVES: Osteogenesis imperfecta (OI) is associated with lung disease due to intrinsic and extrinsic pulmonary defects. We aimed to expand the phenotype of lung disease in a cohort of children and young adults with different OI types.

METHODS: Subjects with OI types III (n=8), IV (n=21), or VI (n=5) underwent pulmonary function tests (PFTs) and chest computed tomography (CT) scans at the NIH CC. For PFTs, arm span and ulnar length measurements were used as height surrogates.

RESULTS: Mean age of subjects with OI types III, IV, or VI was 28.1, 25.2, or 14.5 years, respectively. PFT results were similar using arm spans or ulnar lengths as height surrogates. Air flow parameters were significantly lower in OI type III compared to OI type IV or VI. Regression analysis demonstrated that forced expiratory volume in 1-second (FEV1) correlated negatively with age in OI type IV. Lung volume and gas exchange (diffusion capacity) were significantly lower in OI type III compared to OI type IV or VI. Restrictive lung disease was found in 7/8 OI type III subjects, and half of OI type IV subjects. Most OI subjects had reduced diffusion capacity. CT scans revealed findings in lung airways, parenchyma and extrapulmonary tissue. The most common pulmonary finding was bronchial thickening at the level of small bronchi. CT findings including bronchial thickening (100%, 86%, 100%), atelectasis (88%, 43%, 40%), reticulations (50%, 29%, 20%), ground glass opacities (75%, 5%, 0%), pleural thickening (63%, 48%, 20%) and focal regions of emphysema (13%, 19%, 20%) were detected in OI types III, IV, or VI, respectively, associated with variable whole lung tissue density.

CONCLUSIONS: Utilizing arm spans or ulnar lengths as height surrogates yields similar PFT results. In OI, air flow is reduced, and FEV1 declines with age in type IV OI. Restrictive lung disease is found in young adults with OI type III and half with OI type IV. Abnormal gas exchange and lung structural changes are common in young adults with OI types III, IV, or VI. Bronchial thickening in small airways may be directly related to abnormal collagen or a secondary inflammatory response.

OC23

Boost Brittle Bones Before Birth: A Clinical Trial on Stem Cell Transplantation for Treatment of Osteogenesis Imperfecta

Cecilia Götherström¹, Mikael Sundin^{2,1}, Lilian Walther-Jallow¹, Annika Goos¹, Åsa Ekblad Nordberg¹, Peter Lindgren^{1,3}, Oliver Semler^{4,5}, Magnus Westgren¹, Eva Åström^{6,7}, **BOOSTB⁴ Consortium⁸**
¹Karolinska Institutet, CLINTEC, Stockholm, Sweden. ²Karolinska University Hospital, Section of Pediatric Hematology, Immunology and HCT, Stockholm, Sweden. ³Karolinska University Hospital, Center for Fetal Medicine, Stockholm, Sweden. ⁴University of Cologne, Faculty of Medicine, Cologne, Germany. ⁵University Hospital Cologne, Department of Pediatrics, Cologne, Germany. ⁶Karolinska University Hospital, Neuropediatric Unit, Stockholm, Sweden. ⁷Karolinska Institutet, Department of Women's and Children Health, Stockholm, Sweden. ⁸www.boostb4.eu, Stockholm, Sweden

ABSTRACT

OBJECTIVES: Mesenchymal stem cells (MSCs) is a promising candidate for treating Osteogenesis Imperfecta (OI). The open label, multiple dose, phase I/II BOOSTB4 trial evaluates the safety and efficacy of 4 postnatal or 1 prenatal and 3 postnatal doses of allogeneic fetal MSCs as a treatment of OI type III/severe IV with COL1A1 or COL1A2 glycine substitution.

METHODS: The primary endpoint of the trial is safety and tolerability of intravenous administration of MSCs to the infant and fetus, and safety of the prenatal procedure for the pregnant woman. Secondary efficacy endpoints are: fracture frequency, time to fracture after each dose, growth, mobility, bone mineral density, biochemical bone markers and clinical OI status. The effect on recipient endogenous cells, engraftment of donor cell and Quality of Life are exploratory endpoints. Stakeholder's experience and non-invasive prenatal diagnosis are evaluated.

Both treatment groups are clinically and molecularly diagnosed and receive 4 doses of MSCs at 4-month intervals:

1. Postnatal group: The 1st dose is administered before 18 months of age (n=15).
2. Prenatal group: The 1st dose is administered prenatally (gestation week+day 16+0–35+6) and 3 doses postnatally (n=15).

The treatment groups are compared to matched historical controls. Subjects are monitored in-patient for 48 (dose 1+2) or 24 (dose 3+4) hours after each dose, and out-patient 6 and 12 months after the last dose, and thereafter yearly for 8 years. EudraCT-number: 2015-00369-60, ClinicalTrials.gov: NCT03706482.

RESULTS: The trial is performed in Sweden and has from 7 European countries included all 15 children in the postnatal group and 3 fetuses in the prenatal group. By 21st of April 2022, 42 postnatal and 3 prenatal doses have been administered. Six subjects have received all 4 doses. No serious short-term adverse reactions have been identified in the infant, fetus or pregnant woman.

CONCLUSIONS: To date, 18 subjects have received 1–4 doses of same-donor MSCs with no significant short-term complications. The postnatal group is closed for inclusion, and the prenatal group is paused for inclusion due to funding constraints.

FUNDING: The BOOSTB4 project has received funding from the EU Horizon 2020 research and innovation programme (Grant No 681045), the Swedish Research Council and Region Stockholm.

OC24

Impaired osteoblastogenesis and extracellular matrix formation in an *MBTPS2*-knockout cell-based model of X-linked Osteogenesis imperfecta

Tatyana Danyukova¹, Kenneth Schöneck¹, Timur A. Yorgan¹, Robert Hardt², Jamie Soul³, Dominic Winter², Sandra Pohl¹

¹Institute of Osteology and Biomechanics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. ²Institute for Biochemistry and Molecular Biology, Medical Faculty, University of Bonn, Bonn, Germany. ³Skeletal Research Group, Biosciences Institute, Newcastle University, Newcastle upon Tyne, United Kingdom

ABSTRACT

OBJECTIVES: The site-2 protease (S2P), encoded by *MBTPS2*, is a Golgi-resident intramembrane-cleaving protease. S2P activates a number of membrane-bound transcription factors that are involved in lipid metabolism and response to accumulation of unfolded proteins in the endoplasmic reticulum (ER stress response). Missense variants in *MBTPS2* have been associated with an X-linked recessive form of Osteogenesis imperfecta (X-OI). The exact molecular role of S2P in the pathogenesis of X-OI is still elusive; yet, osteoblasts have been assumed to be affected by S2P deficiency. In this study we aimed to investigate the role of S2P in osteoblast function by using an osteoblast-based model of X-OI.

METHODS: Using CRISPR/Cas9, we generated an *Mbtps2* knockout cell line of mouse calvarial pre-osteoblasts (Δ S2P MC3T3). The knockout was verified by anti-S2P immunoblotting and proteolytic processing of an S2P substrate in the obtained clonal lines. ER stress response was analysed by measuring the expression of *Ddit3* and *Hspa5* and the splicing of *Xbp1* mRNA upon induction with thapsigargin. The expression levels of osteoblast markers were analysed in mutant *versus* control MC3T3-derived osteoblasts (MC3T3^{Obl}) by qPCR, immunoblotting and omics profiling.

RESULTS: Δ S2P MC3T3 cells displayed abnormal ER stress response as evidenced by decreased expression of *Ddit3* and *Hspa5* and sustained splicing of *Xbp1* mRNA upon treatment with thapsigargin. Upon differentiation in osteogenic medium, Δ S2P MC3T3^{Obl} demonstrated a drastically reduced synthesis of collagen type I (Col1). Intracellularly, Col1 was also detected in significantly lesser amounts in Δ S2P MC3T3^{Obl} and appeared to be retained in the ER. Noteworthy, the expression of *Col1a1* and *Col1a2* was unaffected, suggesting posttranscriptional dysregulation of Col1 synthesis in S2P-deficient cells, likely due to Col1 misfolding. The transcript and protein levels of the ER chaperones BiP, PDI and HSP47, involved in the folding of Col1, and the expression of osteoblast markers *Bglap*, *Ibsp* and *Alpl* were significantly decreased in Δ S2P MC3T3^{Obl}. Proteome analysis revealed aberrant formation of extracellular matrix by Δ S2P MC3T3^{Obl}.

CONCLUSIONS: S2P-deficient MC3T3 cells undergo impaired osteoblastogenesis associated with abnormal ER stress response and defective Col1 synthesis and extracellular matrix formation.

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OC25

Anti-Siglec 15 treatment improves trabecular and cortical bone parameters in adult female mice with moderate-to-severe osteogenesis imperfecta

Ketsia Seide¹, Chethana Gallage Dona¹, Stephen B. Doty¹, Alyssa Veneziale², Holly LoTurco¹, Erin Carter¹, Nancy Pleshko², Cathleen Raggio¹

¹Hospital for Special Surgery, New York, USA. ²Temple University, Philadelphia, USA

ABSTRACT

OBJECTIVES: Osteogenesis imperfecta (OI) is a heterogeneous type 1 collagenopathy characterized by bone fragility. Bisphosphonates are recommended to decrease fractures in children with OI, but gaps persist

for effective pharmacological treatment in adults. Our study investigates a monoclonal antibody targeting the sialic acid-binding immunoglobulin-like lectin 15 (Siglec 15) immunoreceptor^[1], NP159 (Nextcure), to improve bone quality and decrease fractures in an established mouse model of moderate-to-severe OI (oim/oim).

METHODS: This reports preliminary data from n=79 female mice (15 wildtype (WT) saline, 16 WT NP159, 8 WT alendronate (ALN), 14 oim/oim saline, 16 oim/oim NP159, and 10 oim/oim ALN) treated with either NP159 (10mg/kg given weekly for one month then biweekly for the remainder), saline (weekly), or ALN (0.21 mg/kg weekly) from 14-26 weeks, under IACUC approval. Calcein (15 mg/kg) and xylene orange (90 mg/kg) labeling were administered at the start and end of treatment, respectively, to evaluate bone growth. Faxitron images at 14 and 26 weeks were taken to evaluate fracture incidence. Tibias, femurs, humeri, and L4-L6 vertebrae were analyzed post-sacrifice for femoral length, histology, microcomputed tomography (micro-CT) analysis and compositional analysis by Fourier transform infrared spectroscopy (FTIR).

RESULTS: At sacrifice, after 12 weeks of treatment, NP159 and ALN treatment decreased fractures in oim/oim mice compared to saline (p<0.05); Even though some Micro-CT determined bone parameters were higher in NP159 treated oim/oim compared to saline, none of these differences reached statistical significance. Histology showed increased endosteal and trabecular osteoid formation, and a decrease in osteoclast number. FTIR showed a normalized mineral: matrix ratio with NP159 and increased acid phosphate (newer mineral) in NP159- and ALN-treated oim/oim compared to WT, and similar carbonate content.

CONCLUSIONS: These preliminary results show that NP159 reduces fractures, increases endosteal bone formation, and normalizes mineral:matrix, which is likely attributable to increased osteoid formation. Mechanical testing will yield insight into whether these cortical and trabecular bone changes are favorable for bone strength. These preliminary results support continuing investigations of NP159 as a promising therapeutic for adults with OI.

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OC26

Syntaxin18 defects in human and zebrafish cause traffic jams and unravel key roles in early bone development

Brecht Guillemin¹, Hanna De Saffel¹, Jan Willem Bek¹, Piyanoot Tapaneeyaphan¹, Adelbert De Clercq¹, Tamara Jarayseh¹, Sophie Debaenst¹, Andy Willaert¹, Peter Byers², Toon Rosseel¹, Paul Coucke¹, Bettina Blaumeiser³, Delfien Syx¹, Fransiska Malfait¹, Sofie Symoens¹

¹University Ghent, Ghent, Belgium. ²University Washington, Seattle, USA.

³University Antwerp, Antwerp, Belgium

ABSTRACT

OBJECTIVES: SNARE proteins comprise a conserved protein family responsible for catalyzing membrane fusion during vesicle traffic. Syntaxin18 (STX18) is a poorly characterized endoplasmic reticulum (ER)-resident t-SNARE. Recently, together with TANGO1 and SLY1, its involvement was shown in ER to Golgi transport of collagen II during chondrogenesis. Currently, STX18 is not linked to any human disease and no animal models are available with STX18 defects.

METHODS: Whole exome sequencing (WES) was applied for a fetus with lethal osteogenesis imperfecta, presenting with multiple fractures, abnormal cartilage formation, tibial bowing, irregularly formed mandible, and severe cranial undermineralization. We performed protein modelling and overexpression studies; and generated zebrafish models deficient for Stx18 (*uppercut18*) to characterize the effects of its loss of function.

RESULTS: WES revealed a homozygous missense variant p.(Arg10Pro) in *STX18*, affecting a critical residue in the cytoplasmic N-terminal alpha-helical domain of syntaxin18, leading to stable mutant STX18 protein. *Uppercut18* zebrafish had severe cranial malformations, curved backbones and underdeveloped fins, and all died at 11-12dpf. Strikingly,

uppercut18 zebrafish revealed impaired cartilage and skeletal development; and interestingly, displayed (1) altered bone remodeling, (2) general upregulated mRNA and protein levels of components acting within the forming Stx18-complex and secretory pathway, and (3) altered swimming behavior including decreased movement and an increased light-to-dark-transition response.

CONCLUSIONS: We establish a link between genetic defects in *STX18* and osteochondrodysplasia, providing evidence of a first link of *STX18* with human disease, thereby expanding the group of SNAREopathies, and suggesting an additional molecular cause for osteochondrodysplasias. Our studies indicate the importance of WES in the clinic and, although further elucidation of the precise chain of events leading to *STX18*-associated disease necessitates the identification of additional patients and research on patient derived tissue specimen, our zebrafish studies clearly demonstrated the crucial role of Stx18 in early skeletal development.

OC27

Allografting is an effective biological method of fixation and increases bone trophicity in osteogenesis imperfecta

Mathilde Gaumé, Sarah El Yahiaoui, **Marine de Tienda**, Georges Finidori, Zagorka Pejcin, Tristan Langlais, Stephanie Pannier
Necker Hospital, Paris, France

ABSTRACT

OBJECTIVES: Osteogenesis imperfecta (OI) in children is responsible for deformities and fractures with an inherent risk of developing non-union. Indications and efficiency of allografting are poorly documented in this specific population. The objective of this retrospective study was to evaluate the efficacy of this technique in the treatment of OI patients.

METHODS: 36 consecutive lower limb allograft procedures (26 femurs and 10 tibias) were performed at our institution between 2011 and 2021 in 22 patients (mean age, 13.3 years). They were listed according to Sillence classification into type III (17) and type IV (5). The indications for the surgery were as follow: fracture (12), correction of deformity (20) or treatment of non-union (4). In all cases, allografting was added to compensate areas of fragility and in 28 cases they were used as a means of fixation to provide structural support and to avoid the need for plate fixation. The duration of bone consolidation and allograft fusion were assessed at regular intervals (first postoperative visit at 6 weeks, 3, 6, 9 and 12 months). Mechanical and infectious complications as well as Gillette functional score were reported.

RESULTS: The mean follow-up was 6.7 years (range, 1 to 10 years). On average, bone consolidation was achieved after 3.3 months and graft fusion in 7.7 months. No allograft-related complications were observed and particularly no secondary displacement after biological fixation. The Gillette functional score was globally improved and remained stable in 3 cases.

CONCLUSION: In this series, allografting in children with OI appeared to be a reliable method of biological fixation, allowed a fast fusion and contributed to increase bone trophicity.

OC28

Anabolic therapies for bone healing of a femoral critical-sized segmental defect in a mouse model of osteogenesis imperfecta

Kyle Kavaseri^{1,2}, David Bertrand^{1,2}, Mayumi Umebayashi^{1,2}, Josephine Tauer^{1,2}, Frank Rauch^{1,2}, Reggie Hamdy^{1,2}, Bettina Willie^{1,2}
¹Shriners Hospital for Children, Montreal, Canada. ²McGill University, Montreal, Canada

ABSTRACT

OBJECTIVES: Long bone deformities in individuals with osteogenesis imperfecta (OI), corrected using osteotomies and intramedullary rodding, often result in bone non-unions. We examined the efficacy of

bone-targeted prostaglandin E2 receptor 4 agonist prodrug (Mes-1022) or adipose tissue-derived stromal vascular fraction (SVF) to enhance healing of a femoral critical-sized segmental defect (CSD) in an OI mouse model.

METHODS: Zoledronic acid pre-treated female oim -/+ and oim +/+ mice (0.05 mg/kg/wk from age 5-9 wks) received a 2 mm defect, stabilized with an external fixator, at 10 weeks of age. The defect received a collagen-β-TCP scaffold (Cerasorb) loaded with either (I) saline, (II) SVF (250k cells from human paediatric donors), (III) Mes-1022 (50µg, once) or (IV) no scaffold, but Mes-1022 administered systemically (25mg/kg, 3x/wk). *in vivo* µCT was performed on days 0, 28, 42, 56, to assess healing (mineralized callus volume: BV, total callus volume: TV, mineralized callus volume fraction: BV/TV) as relative change (Δ) from baseline (day 0). Qualitative histological assessment was performed on paraffin embedded sections. ANOVA and Tukey post-hoc tests were performed, p<0.05.

RESULTS: Systemic Mes-1022 significantly increased ΔBV in oim +/+ mice at 0-42d and 0-56d (0.74±0.52, 0.89±0.65) compared to local saline (-0.15±0.66, -0.22±0.45) and at 0-56d with local SVF (0.03±0.28). In line with this, systemic Mes-1022 significantly increased ΔTV in oim +/+ mice at 0-42d and 0-56d (0.89±0.73, 0.62±0.83) compared to saline (-4.83±3.15, -8.5±2.55) and at 0-56d SVF (-3.77±2.61). Furthermore, systemic Mes-1022 significantly increased ΔBV in oim -/+ mice at 0-56d (0.63±0.42) compared to local saline (-0.33±0.37) or SVF (-0.08±0.39). ΔBV/TV was significantly increased by local Mes-1022 oim -/+ and oim +/+ mice compared to saline and SVF at all-time points. Although none of the treatments resulted in 100% bony bridging, qualitative histological assessment revealed more advanced bone healing with systemic Mes-1022 treatment in both genotypes.

CONCLUSIONS: Systemic and local administration of Mes-1022 enhanced bone healing compared to locally applied saline or SVF. Locally administered SVF demonstrated similar bone healing to saline. Interestingly, irrespective of treatment the OI mice had similar healing to wildtype controls. Quantitative histological analyses are ongoing to ascertain callus tissue composition.

OC29

Unraveling of the ultrastructural features that determine the variability in phenotypic severity in different dominant forms of OI, using the zebrafish as a model

Lauren Sahd^{1,2}, Caitlin Debaene¹, Sophie Debaenst¹, Tamara Jarayseh¹, Hanna De Saffel¹, Myriam Claeys³, Jan Willem Bek¹, Charlotte Gistelinc¹, Frans Rodenburg⁴, Phil Salmon⁵, Eckhard Witten², Ann Huyseune², Björn Busse⁶, Paul Coucke¹, Andy Willaert¹, **Adelbert De Clercq**¹

¹Center for Medical Genetics, Department of Biomolecular Medicine, Ghent University, Ghent, Belgium. ²Evolutionary Developmental Biology, Biology Department, Ghent University, Ghent, Belgium. ³Research Unit Nematology, Biology Department, Ghent University, Ghent, Belgium. ⁴Institute Biology Leiden, Department of Mathematics and Natural Sciences, Leiden University, Leiden, Netherlands. ⁵Bruker Micro-CT, Kontich, Antwerp, Belgium. ⁶University Medical Center Hamburg - Eppendorf, Department of Osteology and Biomechanics, Hamburg, Germany

ABSTRACT

OBJECTIVES: Large phenotypic variability is observed between OI patients carrying different mutations in type I collagen. However, how specific structural mutations determine phenotypic severity is unknown. Therefore, we compared skeletal phenotypes of three OI zebrafish models, carrying different glycine substitutions in type I collagen (*colla1*^{adc124/+}, *colla2*^{mhl5/+}, *colla1a*^{mhl3/+}) that show variability in phenotypic severity. The skeletal phenotype is studied employing a deep phenotyping workflow, by which multiple techniques can be applied on a single individual zebrafish so that the data can be integrated on specimen level, and by which an increasing level of detail is being harnessed with respect to disease severity and specific data on the skeleton.

METHODS: For structural phenotyping whole-mount staining with Alizarin red S for mineralized tissues, scoring deformities, and the random forest model were used. Micro-CT, transmission electron (TEM), and quantitative backscatter (qBEI) analyses were used for ultrastructural phenotyping.

RESULTS: Alizarin red S staining revealed most fractures occurring in *colla1^{adc124/+}* and *colla2^{mhl5/+}* mutants with especially a high frequency of fusions occurring in the *colla2^{mhl5/+}* mutant, whereas the *colla1a^{mhl3/+}* mutant showed a high frequency of compressions. Phenotypic scoring data of deformities was fed into a random forest model that could distinguish each zebrafish OI mutant model with intervertebral disc anomalies as one of the key diagnostic deformities. Micro-CT data indicated a slightly higher tissue mineral density (TMD) for the *colla1a^{dc124/+}* mutant, a significantly higher TMD in the *colla2^{mhl5/+}* mutant, and a lower TMD for the *colla1a^{mhl3/+}* mutant. Bone analysed by qBEI of the *colla1a^{dc124/+}* mutant mainly showed higher Ca-peak values while a higher mineralization heterogeneity was noted in *colla2^{mhl5/+}* and *colla1a^{mhl3/+}* mutants. Ultrastructural analysis showed disorganised collagen fibrils in the *colla1a^{dc124/+}* and *colla2^{mhl5/+}* mutants, with significantly thinner bone in the *colla1a^{dc124/+}* mutant. The *colla1a^{mhl3/+}* mutant showed less disorganised collagen fibrils.

CONCLUSION: We show that specific bone abnormalities result in different phenotypic severities in OI zebrafish models. The *colla1a^{dc124/+}* mutant, representing the most severe phenotype, shows severe skeletal deformities, disorganised thin bone matrix with high mineralisation. The *colla2^{mhl5/+}* mutant shows more variable skeletal deformities and disorganised but highly mineralised bone matrix, while the *colla1a^{mhl3/+}* mutant, representing the mildest phenotype, reveals under-mineralisation.

OC30

Myostatin deficiency in osteogenesis imperfecta mouse models: potential of post- and pre/peri-natal therapeutic strategies to improve musculoskeletal health in osteogenesis imperfecta

Charlotte Phillips¹, Catherine Omosule², Arin Oestreich², Victoria Gremminger¹, Tara Crawford¹, Jason Mastaitis³, Laura Schulz¹

¹University of Missouri, Columbia, USA. ²Washington University, St. Louis, USA. ³Regeneron Pharmaceuticals, Tarrytown, USA

ABSTRACT

Loss-of-function mutations in myostatin (negative regulator of muscle growth) increase musculature in humans and animals, with concomitant increases in bone size and strength. We postulated that while osteogenesis imperfecta (OI) bone material is biomechanically weaker, it can respond to increased muscle load by altering bone geometry and architecture to generate inherently stronger bone. Through genetic and pharmacologic approaches, we decreased myostatin levels in two molecularly distinct mouse models, *oim* and *G610C*. Genetic studies generated mild OI offspring (*+oim* and *+G610C*) which were myostatin deficient (*+mstn*). Both *+mstn +oim*⁽¹⁾ and *+mstn +G610C*⁽²⁾ mice had increased muscle mass and improved trabecular bone microarchitecture relative to their *+oim* and *+G610C* littermates. The *+oim* mice responded more robustly than *+G610C* mice, with *+mstn +oim* having greater femoral biomechanical strength than *+oim*, partially rescuing the OI bone phenotype^(1,2). Post-natal pharmacological inhibition of myostatin by monoclonal anti-myostatin antibody treatment from 5-16 weeks of age improved bone parameters in both *+G610C*⁽²⁾ and the severe *oim/oim* mice. However, bone improvements were not as significant as those achieved with genetic myostatin deficiency, suggesting prenatal and/or early life myostatin inhibition may be critical for maximum efficacy. Genetic studies also demonstrated a beneficial effect of reduced maternal myostatin on skeletal properties in all offspring regardless of genotype. Specifically, *+oim* offspring femora had 32% greater energy to failure when born to *+mstn* dams versus *+oim* offspring born to *+oim* dams⁽³⁾. We further demonstrated reduced maternal myostatin during pregnancy improved bone geometry and integrity in offspring through embryo transfer

studies⁽³⁾. Specifically, *+oim* blastocysts transferred to *+mstn* recipient dams had stronger bones as adults than those transferred to *+oim* dams. Importantly, these findings demonstrate that the maternal *+mstn* effect on offspring bone is conferred by the uteroplacental environment during pregnancy. Reduced maternal myostatin conferred its effects after gestational age E3.5, implicating the uterine environment as a determinant in the programming of offspring musculoskeletal health. The prenatal period represents a new paradigm for bone health and the potential treatment of OI. These findings are the beginning of defining the potential use of pre/peri- and post-natal therapeutic strategies to improve musculoskeletal health in OI.

OC31

Multimodal Treatment for Severe Spinal Deformity in Osteogenesis Imperfecta: Rationale, Outcomes and Complications

Tyler McDonald, Alexander Kuzma, Celestine Shih, Kenneth Rogers, Petya Yorgova, Richard Kruse, Jeanne Franzone, Suken Shah
Nemours Childrens Health, Wilmington, USA

ABSTRACT

PURPOSE: Patients with osteogenesis imperfecta (OI) often develop progressive spinal deformity, which can adversely affect pulmonary function, sitting balance, mobility, self-care, and quality of life. We report the outcomes of treating scoliosis in OI with a multimodal approach using preoperative bisphosphonate therapy to improve bone quality, posterior spinal fusion (PSF) with rib and/or posterior spinal osteotomies, segmental pedicle screw instrumentation, and cement augmentation, followed by early mobilization.

METHODS: Consecutive patients with OI and thoracolumbar scoliosis managed with PSF and pedicle screw augmentation with cement between 2008-2019 at a single institution and at least one year follow-up were included. Radiographic data were collected from pre-operative and most recent follow-up visits. Incidence of surgical site infection (SSI), proximal junctional kyphosis (PJK), implant failure, cement extravasation, or unplanned return to the OR (UPROR) were recorded.

RESULTS: 28 patients met inclusion criteria. The mean age at surgery was 14.9 years with mean follow-up of 45 months. The average number of levels fused was 13.1 and EBL was 1450mL. There was a moderate correlation between number of levels fused and EBL (Pearson's $r=0.4$, $p=0.03$). The median length of stay was 6 days.

Significant improvements were found in major curve magnitude (74° to 37°, $p<0.001$), apical vertebral translation (47mm to 22mm, $p<0.001$), and lower instrumented vertebra tilt (22° to 9°, $p<0.001$) from preoperative to postoperative values. No significant differences were detected for global coronal balance (GCB), thoracic kyphosis (T1-T12), and lumbar lordosis (L1-L5).

There was one SSI (4%; a superficial infection), one implant failure (4%; screw pullout proximally), one instance of PJK (4%), and one occurrence of adding-on of the proximal thoracic curve cephalad to instrumentation (4%). There was no UPROR, cement extravasation, or neurologic deficit in any patient.

CONCLUSION: Patients with OI and scoliosis can be safely treated with a multimodal contemporary approach of preoperative bisphosphonate treatment, creating spinal mobility, pedicle screw fixation, and cement augmentation with low complication rates. This is the largest series to date of patients with OI and scoliosis undergoing modern pedicle screw fixation and cement augmentation.

P1

Significant modifiable risk factors for bone health in patients with osteogenesis imperfecta; the importance of lateral thinking

Artemis Doulgeraki¹, Asimina Galli-Tsinopoulou², Elpis Vlachopapadopoulou³, Iliana Maniadaki⁴, Christina Kanaka-Gantenbein⁵

¹Department of Bone and Mineral Metabolism, Institute of Child Health, Athens, Greece. ²Unit of Paediatric Endocrinology and Diabetes, ^{2nd} Department of Paediatrics, Aristotle University of Thessaloniki, AHEPA University Hospital, Thessaloniki, Greece. ³Department of Endocrinology-Growth and Development, Children's Hospital, P.&A. Kyriakou, Athens, Greece. ⁴Department of Paediatrics, University Hospital of Crete, Heraklion, Greece, Heraklion, Greece. ⁵Division of Endocrinology, Diabetes and Metabolism, ^{1st} Department of Paediatrics, National and Kapodistrian University of Athens, Aghia Sophia Children's Hospital, Athens, Greece

ABSTRACT

OBJECTIVES: To record coexisting disorders potentially affecting the skeleton in young patients with osteogenesis imperfecta (OI), thus improving their overall bone status and wellbeing.

METHODS: Retrospective review of the medical records of paediatric OI patients who are followed at our center, in joint care with other clinics from all over the country, during the period 2012-2019. An analytical search was made for coexisting chronic disorders, not directly related to OI.

RESULTS: 58 medical files were retrieved. Our patients' age ranged between 15 months-18 years and 28 of them were female. Their OI diagnosis was established either clinically or following a genetic work up. Based on their medical history, our cohort was divided into three categories: A) those with no other disorder (56.8 %), B) those with endocrine disorders, including obesity (24%) and C) those with an allergic phenotype (22.4%). More specifically, group B comprised fourteen patients (9 girls) with the following issues: 8 with thyroid dysfunction (five with Hashimoto thyroiditis, two with thyroid hypoplasia, one with hyperthyroidism), 3 with growth hormone deficiency, 1 with pituitary insufficiency, 1 with premature adrenarche, 1 with pubertal delay and 4 with obesity. Their endocrine work up had been performed on clinical grounds. Group C included 11 OI patients with asthma and 2 with eczema, the severity of which was mild or moderate. They all had increased IgE and eosinophilia. Notably, one girl was diagnosed with coeliac disease, following complaints of chronic constipation.

CONCLUSIONS: A detailed history and clinical examination are vital for OI patients, as a considerable percentage will also suffer from endocrine and/or allergic disorders, which are modifiable risk factors for bone health, either directly or indirectly. Addressing the patient as a whole is essential in order to ensure better management, and be aware of possible coexisting diagnosis guided by symptoms and signs.

P2

Effect of bisphosphonate treatment on oral health status of children and adolescents with osteogenesis imperfecta

Artemis Doulgeraki¹, Andreas Agouropoulos², Margarita Gatzogianni³, Georgios Polyzois¹, Helen Athanasopoulou¹, Aikaterini Kavvadia⁴, Sotiria Gizani²

¹Department of Bone and Mineral Metabolism, Institute of Child Health, Athens, Greece. ²Department of Paediatric Dentistry, National and Kapodistrian University of Athens, Athens, Greece, Athens, Greece. ³Department of Paediatric Dentistry, National and Kapodistrian University of Athens, Athens, Greece. ⁴Department of Paediatric Dentistry, European University Cyprus, Nicosia, Cyprus

ABSTRACT

Objectives. Bisphosphonates (BP) are commonly used to treat patients with osteogenesis imperfecta (OI), but data on the effect of this treatment

on the patients' oral health are scarce. We aimed to investigate the effect of bisphosphonates on the oral health of paediatric OI patients.

METHODS. Twenty OI patients, aged 5-16 ys (14 male) were divided in two groups, matched for age and sex ("BP group" vs "non-BP" group). BP children follow a low-dose protocol of zoledronic acid (0.025 mg/kg/6mo, test dose: 0.0125 mg/kg). All patients were assessed for growth (height, weight and BMI Z-scores), dietary and fracture history, bone mineral density with DXA (head, lumbar spine and total body less head) and basic bone profile and were on cholecalciferol (600 IU/d). Parents and children completed a questionnaire on oral health-related habits (brushing, flossing, use of mouth rinses, sweets and sugary drinks consumption, dental visits) and underwent dental clinical examination recording: DMFT, dmft (dental caries), CPI (severity and degree of periodontal diseases), OHI (oral hygiene).

RESULTS. Growth and head BMD were not statistically different between the two groups and their laboratory profile was normal. As expected, BP group, compared to non-BP, had more fractures ($p=0.002$ for long bones, $p=0.009$ for vertebrae) and lower BMD Z-scores of TBLH ($p=0.021$) and LS ($p<0.001$). Both groups had poor clinical oral health parameters. BP group: mean dmft: 2.6 (SD: 3.6), DMFT: 1.6 (SD: 2.5), CPI: 1.6 (SD: 0.5) and OHI: 2.5 (SD: 0.7), caries free: 30%. Non-BP group: mean dmft: 4.1 (SD: 4.8), DMFT: 3.6 (SD: 4.6), CPI: 1.4 (SD: 0.5) and OHI: 2.4 (SD: 0.6), caries free: 10%. There were no significant differences between the groups for all the dental clinical and questionnaire variables. Subgroup analysis revealed no significant correlations between the dental parameters, except for DMFT that significantly correlated with age ($\rho=0.64$, $p=0.04$ and $\rho=0.83$, $p=0.01$ for the BP and non-BP groups, respectively).

CONCLUSION. Dental caries and poor oral hygiene are commonly encountered in OI patients but use of bisphosphonates does not seem to affect their oral health parameters. Nevertheless, regular dental examination is vital, in order to reinforce proper daily habits to maintain good oral health.

P3

Identification of modifier genes underlying intra-familial phenotypic variability in zebrafish OI models using whole exome sequencing and linkage analysis

Tamara Jarayseh, Adelbert De Clercq, Toon Rosseel, Mauro Milazzo, Andy Willaert, Paul Coucke

Center of Medical Genetics, Ghent University Hospital, Department of Biomolecular Medicine, Ghent University, Ghent, Belgium

ABSTRACT

OBJECTIVES: Clinical variability in OI patients carrying an identical causal variant is frequently observed. This suggests that modifier genes contribute to the phenotypic severity through a network of interactions with the causative gene. Zebrafish is known to be a powerful model to study skeletal disorders. They are highly suitable to study intra-familial variability because of a high level of genomic variation, similarity to human, and because high numbers of progeny with the same causal mutation can be obtained. Therefore, the main objective of this study was to identify modifier genes underlying the phenotypic variability observed in existing OI zebrafish models.

METHODS: We studied a mutant zebrafish line carrying a glycine substitution in the *colla2* gene. Deep skeletal phenotyping was done using a combination of X-ray and Alizarin red mineral staining. Exome sequencing of tail fin DNA was performed on a NovaSeq 6000 illumina sequencer, followed by SNP-based linkage analysis using Superlink Online SNP tool.

RESULTS: Deep phenotyping in a large number of *colla2* mutants ($n=18$) obtained from a single set of parents, revealed a wide phenotypic variability in the vertebral column with variable mineralization, fracture incidence, scoliosis, and other skeletal abnormalities. Exome sequencing of the 6 most mildly and 6 most severely affected *colla2* mutants followed by SNP-based linkage analysis, revealed a potentially linked region on chromosome 14 which segregates with the phenotypic severity in the *colla2* OI model. Haplotype analysis revealed that this genomic

region is 3.06 Mb in size and contains 45 protein coding genes. We are currently validating and narrowing down this candidate region in order to identify potential modifier(s). We also aim to apply this strategy in other OI zebrafish models with a variable skeletal phenotype such as the fkbp10a KO zebrafish model.

CONCLUSION: We showed that zebrafish is a promising model for the analysis of modifier genes involved in skeletal diseases, and most likely also in other disorders. Modifier genes represent promising targets for intervening in disease initiation and progression.

P4

Genetic analysis of Osteogenesis Imperfecta in Brazil

Liliane Souza¹, Annanda Holtz¹, Andresa Estevam¹, Erlane Ribeiro², Angelina Acosta³, Renata Lago³, Genoir Simoni⁴, Juan Llerena Jr⁵, Temis Felix¹

¹Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. ²Hospital Infantil Albert Sabin, Fortaleza, Brazil. ³Hospital Universitário Prof. Edgar Santos, Salvador, Brazil. ⁴Hospital Infantil Joana de Gusmão, Florianópolis, Brazil. ⁵Instituto Fernandes Figueira, Rio de Janeiro, Brazil

ABSTRACT

OBJECTIVE: The aim of this study was to report molecular analysis in a large Brazilian Osteogenesis Imperfecta cohort.

METHODS: Cases were selected at the Brazilian Osteogenesis Imperfecta Network, from five different Osteogenesis Imperfecta Reference Centre located in Northeast, Southeast and South of Brazil. Molecular analysis was performed by Ion Torrent with a NGS panel of 18 genes for OI, with 100% coverage for COL1A1 and COL1A2 genes.

RESULTS: Of the 277 registered cases, 243 were probands. Of these, 229 DNA samples were received. Molecular analysis have been completed in 156 cases and variants identified in 121 cases: 65 (53.7%) in COL1A1, 42 (34.7%) COL1A2, 2 (1.7%) IFITM5, 1 (0.8%) CRTAP, 3 (2.5%) in P3H1, 2 (1.7%) in PPIB, 4 (3.3%) FKBP10, 1 (0.8%) in SERPINH1 and 1 (0.8%) in TMEM38B. Twenty six variants were considered novel. In 35 cases, no variants were identified, requiring further analysis.

Of the 65 variants in COL1A1, 25 were quantitative and 40 qualitative, and in COL1A2, 2 quantitative and 40 qualitative. In those cases, 25 were OI type I, 1 type II, 36 type III and 45 type IV. In the IFITM5 gene variants identified, one was the typical OI V variant (c.-14C>T) and the other involved the residue 40 leading to a mild phenotype.

In 12 cases an autosomal recessive inheritance were identified: one in CRTAP (OI type VII), 3 in P3H1 (OI type VIII), 2 in PPIB (OI type IX), one in SERPINH1 (OI type X) and 4 in FKBP10 (OI type XI). Only 6 cases were children from consanguineous couples. A variant in FKBP10 was detected in 3 unrelated and non-consanguineous cases from the same geographic area, suggesting a founder effect.

CONCLUSION: This is the largest OI sample with genetic analysis from Brazil. Clinical and molecular evaluation showed genetic heterogeneity of OI in our country.

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P5

Characteristic modes of failure in single entry telescopic rods: a combined 2 centre experience

India Cox¹, Louay Al-Mouazzen¹, Sabri Bleibleh², Radu Moldovan², Fiona Bintcliffe¹, C E Bache², Simon Thomas¹

¹Bristol Royal Hospital for Children, Bristol, United Kingdom. ²Birmingham Children's Hospital, Birmingham, United Kingdom

ABSTRACT

OBJECTIVES: The Fassier Duval (FD) rod is a 3rd generation telescopic implant for children with osteogenesis imperfecta (OI). Threaded fixation enables proximal insertion without opening the knee or ankle joint, in contrast to other implants. We have reviewed our combined 2-

centre experience with this implant over 12 years, to test the hypothesis that, while technical implantation is less invasive using threads instead of T-pieces, there remain characteristic modes of failure in common with earlier generation implants.

METHODS: 34 children with a mean age of 5 years (range 1-14) with severe OI have undergone rodding of 72 lower limb long bones (27 tibial, 45 femoral) for recurrent fractures with progressive deformity, despite optimised bone health and bisphosphonate therapy. Data were collected prospectively, recording complications and outcomes of each rod over 1.5 – 11 years follow up. Survival analysis was performed to predict rod survival.

RESULTS: 24 cases (33%) required exchange of implants (14 femoral and 10 tibial). This included 11 rods bending with re-fracture and 8 fractures without rod bending. 4 (5%) required re-operation with implant retention due to loss of proximal fixation in the femur; loss of proximal femoral fixation and distal tibial fixation were common and in the case of tibial fixation almost universal, although few of these cases required revision. 4 cases developed coxa vara requiring correction and there was one deep infection. 5 year survival rate, with rod revision as the end point, was 63% (95% confidence interval (CI): 44%-77%) for femoral rods and 64% (95% CI: 36%-82%) for tibial rods.

CONCLUSION: FD rods are easier to implant but do not improve on revision rates reported for 2nd generation T-piece rods. Proximal femoral fixation is problematic in younger children with a partially ossified greater trochanter. Distal tibial fixation typically fails after 2 years. Future generation implants should address proximal femoral and distal tibial fixation to avoid the majority of complications in this series.

P6

Spine care in osteogenesis imperfecta from a distance: single center experience

Alicia McCarthy, Caitlyn Tramontozzi, Cristina McGreal, Ricki Carroll, Michael Bober, Richard Kruse, Suken Shah, **Jeanne Franzone**

Nemours Children's Hospital, Delaware, Wilmington, USA

ABSTRACT

BACKGROUND: Spinal deformities are common orthopaedic manifestations of osteogenesis imperfecta, including scoliosis, kyphosis, basilar invagination, and spondylolisthesis. Progressive deformities may cause significant morbidity and mortality. Historically, surgical treatment showed modest deformity correction, little functional improvement, and up to 50% complications. Recent evaluation of contemporary techniques at our institution has shown improved outcomes and quality of life. Essential to these outcomes is optimization of preoperative management and postoperative care.

PRESENTING PROBLEM: Patients seeking care with us and traveling long distances present unique perioperative management challenges.

CLINICAL MANAGEMENT: These patients are often unable or unwilling to travel prior to surgery. Therefore, most preoperative evaluation is completed by our nurse practitioners via telephone and telehealth, saving in-person care by our team until immediately prior to surgery. Patients submit outside records and imaging for review and provide detailed information regarding medical/surgical history and functional capabilities. Members of our multidisciplinary OI team are consulted as needed to address a patient's pre-operative needs such as extremity management, pulmonary function evaluation, and metabolic bone health optimization. Education is provided on indications/descriptions of operations, risks and benefits, and postoperative care. Post-discharge care is planned early, prior to patient travel. Local providers, either who historically cared for the patient or now newly enlisted, are consulted to help provide perioperative care and communication channels between them and our team are established, with patient/family consent. Postoperative patient care involves a combination of telemedicine visits, phone calls, emails, and in-person visits in conjunction with their local providers. Locally-obtained imaging is also reviewed by our team. Return visits to our institution are determined by patient distance/preference, comfort of local provider and risk of complications.

DISCUSSION: This approach has been used since 2016 in 44 cases to date and has resulted in comprehensive, streamlined care, with no adverse outcomes and high patient/family satisfaction. Occasionally, patients with particularly complex deformities or comorbid conditions have been asked to travel to us for an in-person pre-operative evaluation. Hurdles include licensing restrictions resulting in inability to conduct full telemedicine visits in some states. Pitfalls include potentially missed comorbid conditions that would impact or delay planned surgical procedure.

P7

3D image registration marginally improves short-term in-vivo precision of high resolution peripheral quantitative CT images from adults with osteogenesis imperfecta compared to cross-sectional-area registration

Syedmahdi Hosseinatababaei^{1,2,3}, Nicholas Mikolajewicz^{1,3}, Elizabeth Zimmermann^{1,3,4}, Maximillian Rummel^{1,3}, Catherine Julien^{1,3}, Frank Rauch¹, Bettina Willie^{1,2,3}

¹Research Centre, Shriners Hospital for Children-Canada, Montreal, Canada.

²Department of Biomedical Engineering, McGill University, Montreal, Canada.

³Department of Pediatric Surgery, McGill University, Montreal, Canada.

⁴Faculty of Dental Medicine and Oral Health Sciences, McGill University, Montreal, Canada

ABSTRACT

Purpose: Repositioning error in longitudinal high-resolution peripheral-quantitative computed tomography (HR-pQCT) imaging leads to different bone volumes being assessed over time. To identify the same bone volumes at each time point, image registration can be used. While cross-sectional area (CSA) registration corrects axial misalignment, 3D-registration additionally corrects rotations. Matched-angle (MA) registration can limit interpolation error when 3D-registering micro finite-element (FE) data. A novel 3D-registration method prevents interpolation error during FE by transforming boundary (TB) conditions instead of the images. We compared the precision of HR-pQCT measurements across different registration methods in adults with osteogenesis imperfecta (OI).

METHODS: The radii and tibiae of 29 participants (19-65 yrs, OI-type: I,IV) were imaged twice on the same day with full repositioning. We compared the precision error of different registration methods for Tb.vBMD, Ct.vBMD, Tb.vBMC, Ct.vBMD, Tb.Th, Ct.Th, failure load, stiffness, and apparent modulus.

RESULTS: At the radius, CSA and 3D methods significantly improved the precision of Tb.vBMD, Ct.vBMD, Tb.vBMC, and Ct.Th compared to the unregistered scans. 3D-registered Tb.vBMD had a trend toward higher precision than CSA. All registration methods significantly improved precision errors for apparent modulus. The precision error of failure load was improved using the TB and MA methods, while the precision error of stiffness was improved using all methods except 3D. At the tibia, CSA and 3D methods significantly improved the precision of Tb.vBMD, Tb.vBMC, and Ct.vBMD measures. 3D-registration significantly improved the precision of Ct.vBMD compared to unregistered scans. Apparent modulus was significantly more precise following CSA and MA registrations and trended toward higher precision using 3D-registration. The TB method improved the precision error of failure load compared to the unregistered and CSA methods. Differences between registration methods were nullified after p-value correction. Also, there was no significant difference between the registered and unregistered scans for failure load and stiffness after correction.

CONCLUSION: 3D image registration (3D-TB and MA for microFE) is recommended for longitudinal HR-pQCT imaging in adults with OI. Since our precision errors are similar to those of healthy adults, these results can likely be extended to other populations.

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P8

Generation of Osteogenesis imperfecta stem cell bioresource to decipher disease mechanism and aid drug discovery

Chiara Felicita Sander¹, Dylan Stavish¹, Meena Balasubramanian^{1,2}, Ivana Barbaric¹

¹The University of Sheffield, Sheffield, United Kingdom. ²The Sheffield Children's Hospital, Sheffield, United Kingdom

ABSTRACT

OBJECTIVES: Osteogenesis imperfecta (OI) has been extensively studied in the past, but remains an incurable disease. Progress in understanding the molecular mechanisms and developing therapeutic strategies has been hampered by the lack of suitable human-based *in vitro* models. Obtaining disease-relevant osteoblasts from patients not only requires performing a painful bone biopsy, but osteoblasts do not typically survive long enough outside the patients' body to undergo extensive testing. Recent breakthroughs in stem cell science have enabled novel approaches to obtaining specialised cell types, including osteoblasts. Particularly amenable to disease modelling is the induced pluripotent stem cell (iPSC) technology, whereby patients' cells from skin biopsies or blood samples are reprogrammed to pluripotency using the introduction of just three or four genes into differentiated somatic cells¹.

Here we aim to generate a panel of iPSC lines from patients with different OI genotypes and use them for producing patient-specific osteoblasts in order to investigate the cellular and molecular mechanisms of OI. Further, we aim to establish a high throughput protocol for differentiation to osteoblasts, focused on yielding an accurate *in vitro* model of collagen expression and secretion involved in bone formation in OI.

METHODS: To generate iPSC lines, fibroblasts were acquired from individuals with OI carrying diverse genetic mutations. Patients' cells were then reprogrammed using an mRNA-based approach². To optimise the differentiation protocol of iPSC to osteoblasts, we are using a previously established non-OI iPSC line MIFF-3³. Efficiency and efficacy of osteoblast generation is assessed by Alizarin Red staining as well as qPCR for cell-type specific markers.

RESULTS: Using mRNA transfection, we have generated iPSCs from one patient and are currently characterising this line. Additionally, we are working on optimising the osteogenesis differentiation protocol, by ensuring mesoderm differentiation before inducing osteogenesis with small compounds, including well-established osteogenic differentiation compounds, as well as additional compounds found to support and enhance osteogenesis *in vitro*^{4,5}.

CONCLUSION: Our preliminary data demonstrated that mRNA-based reprogramming approach allows the generation of iPSC lines from fibroblasts of OI patients. We are currently generating further OI iPSC lines that will be highly beneficial in future research of OI.

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P9

Oral health related quality of life in children with Osteogenesis Imperfecta of different ethnic backgrounds

Jasmine May Cachia Mintoff¹, Catherine DeVile², Belinda Crowe², Megan Riddington², Susan Parekh¹

¹Eastman Dental Institute, London, United Kingdom. ²Great Ormond Street Hospital, London, United Kingdom

ABSTRACT

Dental concerns are common in children with Osteogenesis Imperfecta (OI). There is limited evidence on how children of different ethnic groups with OI view their oral health related quality of life (OHRQoL).

OBJECTIVES: To assess and compare the OHRQoL in children with OI aged between 8 and 16 years-old of different ethnic groups.

METHODS: Ethical approval and consent were obtained. The Child Oral-Health Impact Profile – Short Form (COHIP-SF) was used. Additional questions on demographics, including ethnicity, and qualitative questions were added. The questionnaire was completed between January-October 2019. Participant recruitment was from the OI service at Great Ormond Street Hospital. Statistical analysis using MS Excel and SPSS.

RESULTS: 106 children answered the questionnaire with an average age of 11.9 years. There were more males (n=62) than females (n=44), and 31% of this population self-identified as a minority ethnic group. A higher COHIP-SF score indicates better OHRQoL (maximum score, 76). The COHIP-SF has three domains: Oral Health, Functional and Socio-emotional Well-Being.

The median overall score was 59 with an interquartile range of 15 (not normally distributed). The median scores for each group were:

- Combined minority groups (31%) - 59
 1. Asian (13%) – 49
 2. Black (7%) – 57
 3. Mixed (3%) – 60
 4. Other (8%) – 62
- White (54%) – 58
- Did not respond (15%) – 58

Overall OHRQoL scores were not significantly different between ethnic groups., although the Asian population had the lowest median scores overall and across all three domains. When comparing self-reported severity of OI according to minority ethnicity vs white, most self-reported as mild (45% vs 53%). Of those who self-reported as severe, the majority had more severe types of OI such as Type III. There was a significantly higher proportion of minority groups self-reporting as severe OI compared to White (p-value = 0.01). The small number of participants was a limitation of this study.

CONCLUSION: Overall, ethnicity appeared not to have any impact on OHRQoL. Participants from ethnic minority groups were more likely to self-report their OI as severe. Further studies with larger numbers of participants from minority groups are needed to assess whether ethnicity impacts on OHRQoL.

P10

Bleeding assessment in 195 patients with Osteogenesis Imperfecta

Koert Gooijer^{1,2}, Gabriëla Heidsieck¹, Arjan Harsevoort¹, Daniëlle Bout¹, Guus Janus¹, Anton Franken¹

¹Expert Center for adults with Osteogenesis Imperfecta Isala Hospital, Zwolle, Netherlands. ²Departement of Clinical Genetics, Amsterdam Reproductive & Development research institute, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands

ABSTRACT

OBJECTIVES: Osteogenesis Imperfecta (OI) is characterised by bone fragility. Among several features, easy bruising has been reported. There are multiple case reports on haemorrhagic events in OI while population

studies on bleeding tendency in OI are very sparse. This paper describes the clinical aspects of bleeding and bruising in a large cohort of 328 OI patients. The aim of this study is to provide insight in the clinical aspects and therapeutic considerations of bleeding in OI due to surgery, tooth extraction, menstruation and obstetrics.

METHODS: This descriptive cohort study was conducted at the National Expert Center for adults with OI in the Netherlands. Bleeding was assessed by the validated self-bleeding assessment tool (Self-BAT) which has a normal range of score of 0 to+5 for females and 0 to+3 for males. The tool was digitally distributed among 354 adults with different clinically confirmed types of OI.

RESULTS: 195 of 354 invited patients (response rate 60%) with OI type 1 (n=144), OI type 3 (n=17) and OI type 4 (n=43), aged between 18 and 82 years, completed the tool. Self-BAT scores were above the normal range in 42% of all patients. For males Self-BAT scores were increased in 37% with a mean score of 3.7, ranged between 0;18. For females the Self-BAT scores were increased in 44% with a mean of 5.4 and a range of 0;24. No statistical differences in OI subtypes were found.

CONCLUSIONS: Bleeding tendency seems to be a relevant complication in OI patients as this study confirms the presumption of bleeding tendency. There are specific recommendations to clinicians who treat OI patients to consider an assessment of bleeding tendency and use potential interventions to reduce haemorrhagic complications and improve quality of life.

P11

Mechano-regulation of bone formation and mineralization in healthy and type XI Osteogenesis Imperfecta patient-specific 3D bone organoids

Julia K. Griesbach¹, Anke de Leeuw¹, Friederike A. Schulte¹, Tanja Minacci¹, Pei Jin Lim², Matthias Rüger³, Marianne Rohrbach², Cecilia Giunta², Ralph Müller¹

¹Institute for Biomechanics, ETH Zürich, Zürich, Switzerland. ²Connective Tissue Unit, Division of Metabolism and Children's Research Center, University Children's Hospital Zurich, Zürich, Switzerland. ³Department of Pediatric Orthopaedics and Traumatology, University Children's Hospital Zurich, Zürich, Switzerland

ABSTRACT

OBJECTIVES: Bone remodeling is locally regulated by mechanics *in vivo*^[1]. Our lab has developed a patient-specific bone organoid model^[2] for Osteogenesis Imperfecta (OI) that showed significant differences in mineral density distribution compared to organoids from healthy donors. However, the impact of OI on mechano-regulation of the bone formation and mineralization process remains unclear. Our objective was to develop and validate a method to quantify the amount of mechano-regulation in patient-specific type XI OI and healthy bone organoids.

METHODS: Osteoblasts were isolated from a healthy 15-year-old male and a 3-year-old type XI OI female donor. 3D-bioprinted graphene oxide-incorporated cell-laden scaffolds (N=6) were cultured over 56 days in compression bioreactors^[2], subjected to uniaxial cyclic compressive loading (5x/week, 5 min, 1% strain, 5Hz), and monitored using weekly micro-computed tomography (micro-CT). Micro-CT images were converted to Young's modulus for micro-finite element (micro-FE)^[2]. Segmented time-lapsed micro-CT images were registered to identify regions of formation and quiescence on the organoid surfaces. A new surface strain dilation method was used to associate formation and effective strain from micro-FE results across the organoid. Conditional probabilities, area under the curve for the receiver operating curve (AUCROC) scores for bone formation and mean effective strain were evaluated and compared.

RESULTS: OI and healthy organoids demonstrated high mechano-regulation, however, no group-wise significant (p<0.05) differences were found (AUCROC = 0.71 ± 0.04 for OI, AUCROC = 0.76 ± 0.05 for healthy samples). Mean effective strain in formation sites was greater than quiescent sites by 43.1%±13.4% and 45.1%±7.7% in OI and in healthy samples, respectively. Conditional probability curves were

similar across the two groups, where formation was more likely to occur in areas of high loading.

CONCLUSION: We demonstrated and quantified for the first time that bone organoids exhibit mechano-regulation comparable to bone *in vivo*^[1]. Preliminary results indicate that type XI OI has limited impact on mechano-regulation, despite differences in mineral density distribution. Our bone organoid model and quantification of mechano-regulation can be used to develop and test targeted treatment options for OI, shedding light on patient-specific pathomechanisms in functional bone constructs.

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P12

Should Osteogenesis Imperfecta be Labeled as a Low Bone Mass Condition?

Holly LoTurco¹, Quincy Bianchi¹, Ketsia Seide¹, Chethana Gallage-Dona¹, Erin Carter¹, Karl Jepsen², **Cathleen Raggio¹**

¹Hospital for Special Surgery, New York, USA. ²University of Michigan, Ann Arbor, USA

ABSTRACT

OBJECTIVES: Osteogenesis imperfecta (OI) is a type I collagenopathy resulting in disordered connective tissue, bone fragility, and low bone mass¹. This study aims to establish the structural mechanism of low bone mass in OI and evaluate differences by sex, OI type, or bisphosphonate treatment.

METHODS: This IRB-approved retrospective study included 493 AP hand/wrist radiographs from 385 individuals (154M, 231F) with OI (patients at HSS and in the Brittle Bone Disorders Consortium U54 AR068069). Second metacarpal length, midshaft width, cortical thickness, robustness (total area/length), and relative cortical area (RCA, cortical area/total area) were measured. Bisphosphonate treatment <2 years of radiograph was noted. OI measurements were compared to 541 radiographs from 98 controls (50M, 48F). Non-parametric Kruskal-Wallis tests were conducted ($p < 0.05$).

RESULTS: Average age of OI and control populations were 21.4 ± 18.8 (0 months-87.8 years) and 6.5 ± 5.1 (3 months-18.1 years), respectively.

OI bones showed decreased robustness ($p < 0.001$) and increased RCA ($p < 0.001$) compared to controls. Males with OI had higher robustness than females with OI ($p < 0.05$). Just under half of the cohort (178/385, 46.2%) was treated with bisphosphonates, including types 1, 3, 4, 5, 6, 8, 9, and unknown types. Those not treated with bisphosphonates (207/385, 53.8%) included all represented OI types (1, 3, 4, 5, 6, 7, 8, 9, 13, and unknowns). Treated individuals had lower RCA ($p < 0.001$) and robustness ($p < 0.001$) than untreated individuals. Types 3 and 4 had lower RCA and robustness when treated; people with type 1 displayed no treatment effect.

CONCLUSION: Compared to controls, individuals with OI had decreased robustness indicating slender and structurally weaker bones. However, RCA increased, which is the expected bone mass accrual for slender bones. Treatment was associated with reduced, not increased, bone mass. Our data is inconsistent with classifying OI as a low bone mass condition, which could have important clinical implications.

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P13

Surgical Correction of Skeletal Malocclusion in Osteogenesis Imperfecta

Joseph Napoli

Children's Hospital of Philadelphia, Philadelphia, USA. University of Pennsylvania, Philadelphia, USA

ABSTRACT

BACKGROUND: Skeletal malocclusion refers to improper relationship of the maxillary and mandibular teeth due to mismatch in the size or misalignment of the upper and lower jaws. The estimated prevalence of malocclusion in the general population is 28%. The prevalence is much higher in patients with osteogenesis imperfecta (OI), particularly class III malocclusion with a prevalence greater than 70%.

PRESENTING PROBLEM: Skeletal malocclusion can affect the appearance of the face and cause functional impairment which often cannot be corrected with orthodontic treatment alone. The most common functions affected are breathing, eating, and speech.

Both size and position of the maxilla can cause or contribute to obstructive sleep apnea. Skeletal malocclusion affects eating by interfering with biting and mastication. The effect of malocclusion on speech has been well documented. The articulation of speech sounds is affected, particularly sounds such as “s”, “z”, “sh”, “ch”, and “f”, which can lead to speech sound distortions.

CLINICAL MANAGEMENT: Surgical procedures can correct the aesthetic imbalance in facial appearance and correct functional impairment caused by malocclusion. Conventional techniques in orthognathic surgery can be applied to most skeletal malocclusions in OI, either on the upper jaw, the lower jaw, or both (Rosén et al., 2011). For severe malocclusion, distraction osteogenesis can be used alone (Black and Denny, 2015) or in combination with conventional orthognathic surgery (Napoli and Scotland, 2018). Patients benefit most when the surgeon works with the orthodontist to manage both the tooth position as well as the jaw position. These procedures are done under general anesthesia and usually require an in-hospital stay of 1-4 days. Clinical cases will be presented.

DISCUSSION: Patients with OI may benefit from surgical treatment of skeletal malocclusion to improve appearance and function. Surgical enlargement and repositioning of the maxilla can improve breathing and alignment of the jaws can improve appearance, eating, and speech.

Orthognathic surgery and distraction osteogenesis are safe and effective procedures in patients with OI to achieve these goals.

P14

Assessing the Safety and Efficacy of Tranexamic Acid Usage in Osteogenesis Imperfecta Patients Undergoing Femoral Rodding

Vincent Eaton¹, Makayla Schissel², Elizabeth Strudthoff^{3,2}, **Maegen Wallace^{2,3}**

¹Creighton University, Omaha, USA. ²University of Nebraska Medical Center, Omaha, USA. ³Omaha Children's Hospital, Omaha, USA

ABSTRACT

OBJECTIVES: Due to increased fracture burden and bone deformity caused by Osteogenesis Imperfecta (OI), these patients tend to have numerous operations throughout their life. In addition to skeletal manifestations, there is a potential increase in bleeding susceptibility due to the increased frequency of orthopedic procedures, warranting investigation into methods to mitigate this risk.

This study aims to evaluate the safety and efficacy of tranexamic acid (TXA) usage to reduce intraoperative blood loss in children with OI. We want to assess the potential benefits, risks, and complications involved with TXA use in this patient population. We hypothesize that TXA use will decrease intraoperative blood loss and associated complications in OI patients undergoing femoral rodding.

METHODS: TXA-receiving patients (cases) were matched 1:1 with non-TXA receiving controls on the following criteria: age within 2 years, bone category, and OI Type. Descriptive statistics were used to summarize the data. Fisher's Exact Test was performed to compare transfusion status between groups. A Wilcoxon Rank Sum test was performed to assess differences between the groups in days of stay, length of surgery, and EBL. All analyses were conducted using SAS version 9.4. $P < 0.05$ was considered statistically significant.

RESULTS: Our TXA-receiving population of 30 patients consisted of 11 females and 19 males. 1 patient was OI type I, 13 were OI type III, 14 were OI type IV, and 2 were categorized as other (not Type I through Type IV). We found a significant difference in transfusion status ($p = 0.02$), with no TXA patients requiring a transfusion compared to 20% of the control cases. There is also a significant difference in median EBL ($p = 0.0004$) between groups, with TXA patients having decreased intraoperative EBL (20 mL versus 62.5 mL). There was also a difference in median days of post-operative stay between TXA receiving and non-TXA receiving patients ($p = 0.001$; 2.6 versus 4 days).

CONCLUSIONS: Our study concluded that TXA use in this patient population is associated with lower perioperative transfusions and intraoperative blood loss rates. These results support the standard usage of TXA in these patients to reduce intraoperative blood loss.

P15

Therapeutic use of Indomethacin in Osteogenesis Imperfecta Type V

James Law^{1,2}, Kiran Basraka¹, Lizzie O'Sullivan¹, Vrinda Saraff¹, Nick Shaw¹

¹Birmingham Children's Hospital, Birmingham, United Kingdom. ²Nottingham Children's Hospital, Nottingham, United Kingdom

ABSTRACT

BACKGROUND: Osteogenesis imperfecta type V has a distinctive phenotype of interosseous membrane calcification and hyperplastic callus (HPC) formation. HPC formation typically enlarges then stabilises followed by resolution or further progression which may lead to deformation and/or fractures. The mechanism underlying these features is not fully understood but may be related to a pro-inflammatory state. We present our experience using indomethacin in twin sisters with OI type V.

PRESENTING PROBLEM: They were born at 36-weeks' gestation weighing 1.6 and 1.5 kg and presented with rib and long bone fractures in the neonatal period. Genetic analysis identified mutations in the IFITM5 gene. Bisphosphonates (pamidronate then, later, zoledronate) were started from 6-months old by which time they already had extensive lower-limb callus formation.

At 9 years old, they were independently mobile with no significant functional deficit. However, by the age of 11 years they had developed flexion deformities at their knees and elbows resulting in limited mobility necessitating the use of attendant-propelled wheelchairs. They were referred for powered wheelchairs which would have required substantial adaptations to the family home. A discussion was had regarding a trial of indomethacin following positive experience of its use in another unit.

CLINICAL MANAGEMENT: Following initiation of indomethacin (25mg twice daily for four months then once daily), there was a rapid improvement in six-minute walk test (6MWT) from 40 / 36 metres to 370 / 378 metres with significant improvements in posture, gait and range of movements. Functional ability (Pedi-CAT and MCHAQ) and pain (Visual Analogue Score) also improved.

ESR and CRP, which were raised, appeared to decline following initiation of treatment, but rose slightly after the dose reduction. There was no definitive change in HPC on knee radiographs.

DISCUSSION: We present here detailed functional, physiological, radiological and biochemical assessments showing a clinical improvement associated with indomethacin. Both patients rapidly saw a marked functional and quality of life improvement. Reproducibility

and the mechanism of action remains to be determined as do optimal timing and dosing. However, our experience suggests that indomethacin may be an important therapeutic option in patients with OI type V.

P16

Quality of life in Osteogenesis Imperfecta: evaluation of the content validity of the OIQoL questionnaire in an international cohort

Claire Hill

Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom

ABSTRACT

OBJECTIVES: Osteogenesis Imperfecta (OI) is a rare hereditary condition characterised by bones that break more easily, hypermobility, short stature and deformity. Quality of life (QoL) is a multifaceted concept described in different ways by different people at differing times in their life. As a result it can be complex to measure and difficult to describe and explain.

The OIQoL questionnaire was developed using bottom up methodology and followed Food and Drug Administration guidelines. Development took place within the UK, which has a particular set of environmental, social and economic circumstances that could well impact on the content of the questionnaire. This multi-centre international study aimed to explore quality of life in children with OI, comparing the emergent themes to those previously identified in the UK and examining the content validity of the OIQoL questionnaire.

METHODS: Qualitative focus groups of young people, with OI were undertaken in eight countries; Belgium, Chile, China, France, Italy, Germany, the Netherlands and Russia, between July and October 2019. The aim of the study was two-fold: encourage children and young people, outside of the UK, to talk about living with OI; and to ask participants to examine the OIQoL questionnaire, ascertaining their opinion with regards to the content. Focus groups were audio-recorded, transcribed and translated.

RESULTS: All participating countries acknowledged several topics which were important to their QoL: having friends and family; socialising; having a good home and school environment. Taking care, moving safely to avoid fractures and having to pre-assess situations and environments were acknowledged as negative impacts of OI.

CONCLUSION: This international, multi-centre study demonstrated that countries outside of the UK describe similar impacts on QoL as a result of OI. This research highlights some redundant and repetitive items within the OIQoL questionnaire, suggesting it would benefit from revision and shortening. However the conceptual framework^[1] appears to remain valid when describing QoL in children and young people with OI.

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P17

What are the perceived therapy needs of adults living with Osteogenesis Imperfecta? A focus group study

Sophie Barlow¹, Prof Richard Keen¹, Anju Jaggi¹, Lucy Dove², Gregory Gregory Booth¹, Dr Judith Bubbear¹

¹Royal National Orthopaedic Hospital, Stanmore, United Kingdom. ²Oxford University Hospital, Oxford, United Kingdom

ABSTRACT

OBJECTIVES: Osteogenesis Imperfecta (OI) is a rare genetic disorder of collagen characterised by fragile bones. The clinical presentation includes musculoskeletal disorders, chronic pain and mental health issues which impact on quality of life. To date there is no published data on what adults with OI perceive their therapy needs to be. This study

aims to explore these therapy needs and may inform future service design.

METHODS: A convenience sample of adult patients (aged > 18 years) were recruited from multidisciplinary OI clinic.

Participants were consented, given a time and link for a video discussion. They were split into two groups based on their clinical Silences classification and severity of OI.

Four semi-structured questions were asked focusing on their perceived needs for therapy.

Braun and Clarke's thematic analysis method (2006) was used to identify commonly occurring themes from the focus group data.

RESULTS: In total, eleven participants were allocated to two focus groups and their ages ranged from 27-68 years. The discussions from both groups elicited similar themes which were: previous experience of accessing healthcare, OI across a life span and a vision for an optimal service.

There was an overwhelming consensus that therapy was required in adults with OI and treatment was not just for fractures. This included physiotherapy, occupational therapy and psychology to support these participants wide ranging needs.

The participants valued continuity of care with healthcare professionals who understood OI.

The participants reflected on having holistic treatment to help manage their condition.

Transition from childhood to adult services was challenging and participants who had experienced an MDT clinic valued the breadth of care provided especially as they aged.

Gender differences were discussed in relation to childbearing and menopause.

CONCLUSIONS: The discussions reflected the life-long nature of OI and the impact it has on participant's quality of life as they age. Accessing therapy was disjointed. Due to the complexity and variability of OI, the participants felt a holistic approach to treatment was the most beneficial. This study lends strength for a specialist multidisciplinary service to be commissioned for adults with OI in order to provide holistic, patient centred care.

FUNDING: from Brittle Bone Society Grant

P18

A service evaluation examining the clinical application of the; Bleck, Brief Assessment of Motor Function Lower Limb and the Screening Tool for Everyday Mobility and Symptoms (STEM) in the functional assessment of children aged 6-18 years who have Osteogenesis Imperfecta

Caroline Marr, Claire Hill, Davina Ford
Sheffield Children's NHS Foundation Hospital, Sheffield, United Kingdom

ABSTRACT

OBJECTIVES: Osteogenesis Imperfecta (OI) is a disease with varying severity affecting the physical, social and emotional wellbeing of the child and their family. It is a rare hereditary condition affecting approximately 1 in 20,000 births.

During admissions at Sheffield Children's hospital all children and young adults (CYA) aged 6-18 undergo a physical function assessment. Current practice is to utilise the Bleck or modified Brief Assessment of Motor Function Lower Limb (BAMFLL). The aim of the service evaluation was to determine if the Screening Tool for Everyday Mobility and Symptoms (STEMS) could provide clinically relevant information, replacing the aforementioned assessments.

METHODS: Over a 6-month period, a convenience sample of 29 CYA with OI were assessed using the BLECK, BAMFLL and STEMS.

RESULTS: Of the 29 participants; 18 had mild, 4 moderate and 7 severe OI. In the mild group, there was a ceiling effect with the Bleck, with all

participants' achieving full marks. Most scored full marks on the BAMFLL, though 5 were unable to run. With the STEMS, fatigue was reported as the most limiting factor of physical function. In those with moderate OI, 3 were ambulant and achieved full marks on the Bleck. As in the mild group, the BAMFLL provided some distinction between the ambulant participants, with 2 being unable to run. With the STEMS, fatigue was a limiting factor in the home. In the community and school, pain and fatigue limited activities. The data in the severe group was more mixed. Both the Bleck and BAMFLL provided information on ambulation status. With the STEMS only 2 children were independent walkers in the home, with most using wheeled mobility across the 3 environments. Most reported no problems. When difficulties were noted, fatigue was the most limiting factor.

CONCLUSION: The service evaluation demonstrated that the STEMS provides clinically relevant information for children with OI. As the Bleck seemed to have a ceiling affect in the milder cohort, this assessment may-not be clinically useful for the more ambulant CYA. For assessment of physical function, a combination of the BAMFLL and STEM may provide the most clinically relevant picture.

P19

Insight into the bone mechanism of *CRTAP*-null osteoblasts

Aileen Barnes, Apratim Mitra, Ryan Dale, Joan Marini
National Institutes of Health, Bethesda, USA

ABSTRACT

OBJECTIVES: Osteogenesis imperfecta (OI) is a collagen-related heterogeneous bone dysplasia characterized by easy fracture susceptibility and short stature. Type VII OI is caused by recessive null mutations in *CRTAP* (cartilage-associated protein), a component of the type I procollagen 3-hydroxylation complex. Type VII OI is almost invariably lethal in the first year of life. Due to early lethality, little is known about how *CRTAP* mutations cause bone dysplasia in OI. We studied the osteoblasts of non-lethal siblings with *CRTAP*-null mutations to gain further insight into its osteoblast mechanism.

METHODS: Differentiated osteoblasts were analyzed by RNA-Seq and qPCR. Collagen modification, proliferation assays and westerns blots were performed in fibroblasts and osteoblasts from non-lethal and lethal *CRTAP* cases.

RESULTS: Collagen overmodification and chaperone levels were similar in fibroblasts from both lethal and non-lethal probands. RNA-Seq of differentiating *CRTAP*-null osteoblasts showed high upregulation of gene ontology pathways involved in DNA replication and cell cycle genes. BrdU incorporation confirmed ~2x increased proliferation in non-lethal proband osteoblasts, in contrast to decreased proliferation of fibroblasts from probands with both lethal and non-lethal *CRTAP* mutations. In addition, cyclin dependent kinase inhibitor 2A (*CDKN2A*), a regulator of two important cell cycle proteins involved in cell cycle inhibition at the G1-S checkpoint, was significantly reduced (>50%) in *CRTAP*-null osteoblasts, while expression of cyclin B1 (*CCNB1*), which regulates the G2-M checkpoint, was enhanced. Ossification and bone and cartilage development gene ontology pathways were upregulated throughout differentiation. In mature *CRTAP*-null osteoblasts, *ALPL*, *SP7*, *BGLAP*, *IBSP*, and *MEPE* transcripts were significantly increased and confirmed by qPCR. Ingenuity pathway analysis suggested an upregulation of BMP2 signaling, supported by increase of both *BMP2* and *DLX3*, an early BMP2-responsive gene which promotes proliferation and induction of osteogenic markers, on RNA-Seq and qPCR. Throughout differentiation, *CRTAP*-null osteoblasts showed a decrease in gene ontology pathways involved in cell adhesion and extracellular matrix organization.

CONCLUSIONS: *CRTAP*-null osteoblasts have increased expression of mineralization genes vs control. *CRTAP*-null osteoblasts also have increased proliferation, shown by increased BrdU incorporation and altered regulation of cell cycle transcripts. Increased proliferation and osteogenesis of type VII OI osteoblasts may be stimulated through upregulation of BMP2 signaling.

P20

Severe Obesity in Osteogenesis Imperfecta - What are the Treatment Options?

Jannie Dahl Hald^{1,2}, Jens Meldgaard Bruun^{3,4,5}, Torben Harsløf¹, Bente Langdahl¹

¹Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark. ²Center of Rare Diseases, Pediatric and Adolescent Medicine, Aarhus University Hospital, Aarhus, Denmark. ³Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus, Denmark. ⁴Department of Clinical Medicine, Aarhus University, Aarhus, Denmark. ⁵Danish National Center for Obesity, Aarhus, Denmark

ABSTRACT

BACKGROUND: Osteogenesis imperfecta (OI) is characterized by fractures, and immobilization, which may lead to obesity, as increasing energy expenditure is challenging in OI.

Roux-en-Y gastric bypass (RYGB) surgery is an effective treatment for severe obesity. However, bariatric surgery causes decreased mechanical loading on the skeleton and malabsorption which decreases bone mass and is therefore in general not recommended in OI. Importantly, literature on the area is sparse.

PRESENTING PROBLEM: A 49-year-old woman with OI type I due to a COL1A1-mutation, who also suffered from obesity, BMI 43 kg/m², and decreasing mobility. Dietarian consults were unsuccessful. She had degenerative arthrosis, no type 2 diabetes or sleep apnea. She had suffered multiple vertebral and non-vertebral fractures throughout life.

CLINICAL MANAGEMENT: She was treated for one year with Setrusumab (Asteroid clinical trial) followed by zoledronate for two years. She was increasingly physically restricted due to obesity and was eventually referred for a gastric bypass. BMD T-scores were in the normal range; biochemical bone markers were suppressed. She lost 8% body weight preoperatively as recommended and ceased smoking. She underwent an individualized follow-up with DXA, HRpQCT, and biochemistry perioperatively and after 6 months, and annually after surgery.

RYGB surgery was without complications, and one year postoperatively she had lost 40 kg body weight, BMI 28 kg/m². Calcium, vitamin D3 and PTH levels remained within the normal range, procollagen type 1 N-terminal propeptide (PINP) and carboxy-terminal collagen crosslinks (CTX) increased to low-normal values, and DXA BMD decreased by 3.6% and 4.3% at the lumbar spine and total hip, respectively. D100 and BV/TV remained unchanged, whereas Tb.N decreased by 20%, and Tb.Sp increased 23%.

DISCUSSION: In OI optimized bone health is constantly sought to prevent the next fracture. Yet, general physical and mental well-being is essential. Weight control is challenging, and bariatric surgery is controversial. In this case bone anabolic treatment followed by bone protective treatment had been timed in order to minimize deterioration. This case shows that RYGB may be considered in milder OI phenotypes despite an increased risk of fractures. Close cooperation between experts within the medical fields must be enforced.

P21

Crispant analysis in zebrafish as a tool for rapid functional screening of disease-causing genes for Osteogenesis Imperfecta

Sophie Debaenst, Hanna De Saffel, Jan Willem Bek, Adelbert De Clerck, Tamara Jarayseh, Lauren Sahd, Paul Coucke, Andy Willaert
Ghent University, Ghent, Belgium

ABSTRACT

OBJECTIVES: Osteogenesis imperfecta (OI), characterized by skeletal deformities, is a genetically heterogeneous connective tissue disorder mainly caused by autosomal dominant mutations in collagen type 1. Mutations in non-collagen genes are mostly associated with recessive forms of OI and encode proteins involved in osteoblast differentiation,

bone mineralization and collagen processing. However, the genetic spectrum of OI is expanding and the underlying pathogenic mechanisms are often not yet known. To quickly gain insight into these mechanisms, we aimed to develop a rapid and cost-effective approach for *in vivo* functional validation of OI-causing genes, using the zebrafish model system. This model is attractive to study skeletal diseases due to its easy genetic manipulation and genetic similarity to humans.

METHODS: We used the so-called crispant screening approach, based on CRISPR/Cas9 technology, in order to phenotype directly in FO mosaic founder zebrafish. Crispants significantly reduce model generation time, enabling the validation of a large set of genes in a short period of time.

RESULTS: We selected a panel of 6 OI genes (creb3l1, ifitm5, mbtps2, sec24d, serpinf1 and sparc) and micro-injected CRISPR/Cas9 components (gRNA/Cas9) targeting the gene of interest, in one-cell stage zebrafish embryos with an osteoblast-specific Tg(osx:Kaede) transgenic background. NGS analysis revealed out-of-frame efficiencies higher than 70%, indicating a high fraction of knock-out alleles and thus resembling a stable knock-out model. Phenotypic analysis was performed at 14 and 90 days after fertilization, though fluorescence microscopy (osteoblasts), alizarin red bone staining and micro-CT analysis for quantitative analysis of the skeleton. Crispants for creb3l1, coding for OASIS, which has an important role in osteoblast differentiation during bone development, show skeletal abnormalities, such as vertebral fusions, callus formation in the vertebral arches indicating previous fractures and ectopic mineralization at 90 dpf. These investigations are also ongoing for the remaining 5 genes.

CONCLUSION: Taken together, we showed that crispant screening in zebrafish is a promising approach for rapid functional screening of OI candidate genes. Moreover, the crispants have the potential to provide new insights into the role of these genes in skeletal biology and can be used as a tool for osteogenic compound screening.

P22

"O.I. wish orthopaedic surgeons had better strategies to help with..." - results of a patient and parent-based survey

Jill Flanagan¹, Jeanne Franzone², Erika Carter³, Tracy Hart³, Laura Tosi⁴, Maegen Wallace⁵

¹Children's Healthcare of Atlanta, Atlanta, USA. ²Nemours Children's Hospital, Wilmington, USA. ³OI Foundation, Gaithersburg, USA. ⁴Children's National, Washington DC, USA. ⁵University of Nebraska Medical Center, Omaha, USA

ABSTRACT

Osteogenesis Imperfecta (OI) is a genetic disorder caused by a mutation in type I collagen, characterized by bone fragility and deformity. Current treatment methods are focused on decreasing fracture rates, and improving overall global function. Recent orthopaedic surgery research has focused primarily on fracture fixation and outcomes of intramedullary rodding of long bones. While surgical techniques continue to evolve and improve, recent trends are also focusing on patient quality of life and patient-reported outcomes measures (PROM).

The authors created a 12-question survey with the OI Foundation (OIF) which sought to gather information regarding the aspects of orthopaedic care OI patients and families feel to be the most pressing to improve. The survey was electronically administered by the OIF and the OI Federation Europe (OIFE) to all members. 341 individuals completed the survey. The final question of the survey indicated, "Please include any comments you would like to pass along." Responses to this question were grouped into themes.

Many of the survey questions we asked were related to childhood orthopaedic surgical interventions. However, 75% of the respondents who answered the age question (254/335) were adults.

16% of respondents recall that they have been told that they could not have surgery on a long bone because they were too young. Of the 16%, 37.8% were told that <5 years was too young, 13.4% <4 years was too young, and 48.8% < 3 years of age was too young. Nearly 22% of respondents were told that their bones were too small to have

intramedullary fixation. We cannot assess if this is what patients were told before or after more modern implants were available.

The information collected helps reveal trends of the typical orthopaedic advice patients and families receive. The responses help elucidate the topics requiring focus for the improvement of OI orthopaedic care. Patient concerns and insights most powerfully drive the research questions we should ask to advance the orthopaedic care of OI patients.

This survey helps reveal trends of the typical orthopaedic advice patients and families with OI receive. Having the details of the survey and the responses help guide future orthopaedic PROMs in the arena of OI clinical and surgical care.

P23

Physical activity of children with osteogenesis imperfecta during the period of immobilization (fractures) and during the «light» period (period of full functioning)

Nadezhda Epishina

Charitable Foundation "Fragile People", St. Petersburg, Russian Federation

ABSTRACT

OBJECTIVES: The study will qualitatively assess the levels of physical activity of children in different periods of life. This will help to develop rehabilitation strategies and plan intervention in the future. Based on the results of this study, it will be determined if new stage of research on the rehabilitation strategy is needed.

METHODS: 4 physical therapists, 8 children aged 10-15 (4 girls and 4 boys).

Children correspond to the 3-4 level of the functional classification scale of the movement abilities and self-service in OI (proposed by N. Epishina)

Selection of scales, questionnaires, tests for assessing physical activity, their adaptation, final analysis, including criteria for the physical activity pie.

Questionnaires, tests, zoom meetings, interviews (including physical self-image assessment questionnaires, pain assessment, kinesiophobia).

Specialists adapted the questionnaire on physical activity, which must be filled out 2 times: during the "light" period and the period of immobilization. The questionnaire contains data on the functional level, the results of the Hare scale and adopted FMS test.

Children keep diaries during the week. These are questionnaires and questions about physical activity relevant to the condition, adapted individually for each child.

Results. The study period is March - June 2022. We expect to receive the following result during the study: 3 pyramids of physical activity during the immobilization period, during the "light" period and the norm.

The conclusion is made about the level of motor activity in children in different periods of life, we will evaluate how pain, fatigue, the level of physical self-esteem affect the level of motor activity. What factors should be taken into consideration by PT when he/she is developing a rehabilitation program for a client depending on the period.

P24

Investigating the transition from paediatric to adult services and the management of ongoing care of adults for osteogenesis imperfecta: A qualitative study

Chloe Morgan, Laura Wilkinson, Darren Edwards, Joy Merrell

Swansea University, Swansea, United Kingdom

ABSTRACT

OBJECTIVES: In the UK, children with Osteogenesis imperfecta (OI) can be seen in one of six specialist centres, however, there are currently no specialist services offered to adults with OI. The aim of this research

was to investigate the transition from paediatric to adult services and the management of ongoing care of adults for osteogenesis imperfecta.

METHODS: This qualitative study consisted of one online focus group and two one-to-one online interviews. Four females and two males participated, the age of the six participants ranged from 26 to 66, OI types I, III and IV were represented and England, Wales and Northern Ireland were represented in the sample. A topic guide was used to guide the conversation with open-ended questions to encourage discussion. Inductive thematic analysis was conducted with rigour established via researcher triangulation.

RESULTS: There were four themes identified, each of the themes contained three sub-themes. The "Knowledge" theme identified issues relating to a lack of understanding of OI, both by individuals with the conditions and by the HCP's responsible for treating the condition. The "Experiences of care" theme included issues relating to how experiences in both paediatric and adult health services affected participants emotionally and the difficulties arising from a lack of continuity in health care. The "Being proactive" theme indicated that self-advocacy was important in ensuring people with OI get the right care and that utilising the OI community plays a significant role. Finally, the "Health care needs" theme highlighted that support and communication with HCP's is vital and that ensuring access to the correct services is critical.

CONCLUSIONS: These findings have implications for practice and policy, although the sample size was small and more research is needed in order to establish whether the experiences of these participants reflect that of the wider OI population in the UK.

P25

Service evaluation reviewing the application of the Bayley Scale of Infant and Toddler development in children with severe, complex and atypical Osteogenesis Imperfecta

Caroline Marr

Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom

ABSTRACT

Osteogenesis Imperfecta is a rare hereditary condition affecting approximately 1 in 20,000 births. Developmental delay is seen in children with the condition. Assessment is key in ensuring appropriate interventions. Although not a disease specific measure, the Bayley Scale of Infant and Toddler Development (BSITD) is used in clinical practice by the Sheffield Children's Hospital team to assess development in children with with severe, complex and atypical Osteogenesis Imperfecta (SCAOI).

OBJECTIVES: To retrospectively review BSITD assessments, completed in children with SCAOI, who received care at Sheffield Children's NHS Foundation Trust from January 2017 to August 2020, in order to determine if there are any patterns that emerge across the assessments.

METHOD: A retrospective analysis of BSITD assessments, between January 2017 and August 2020, in children with SCAOI.

RESULTS: A total of 19 BSITD assessments, from 10 patients, were included. 14 of the assessments were with children with type III OI; 5 had type V OI. Mean age was 19 months 17 days. Of the 19 assessments 4 were incomplete, reasons included; fatigue, lack of interest and time limitations. Application of the regression rule was noted in all subsections. Manipulating blocks, squeezing objects, removing lids, instigating play, using words appropriately to make needs known, establishing head control, prone lying and sitting were tasks across the assessments that children repeatedly failed. Only 4 assessment scored above the 50th percentile in the cognitive subsection, with 10 scoring below the 24th percentile. In the language subsection 2 assessments scored above the 50th percentile, with 9 below the 24th percentile. In the motor subsection none of the assessment scores were above the 50th percentile, with 15 assessments below the 24th percentile.

CONCLUSION: In clinical practice parents of children with SCAOI are told to expect a delay in their child's gross motor acquisition. The service evaluation supports this statement whilst suggesting that within this

patient group developmental delay can be observed in all subsections. Further investigation with a larger cohort is warranted to determine, if the BSITD is the appropriate tool to use and establish if the delay observed is a true reflection of children with SCAOI.

P26

Cross-centre psychology collaboration on the adaptation of young person 'tree of life' narrative therapy groups to online during the COVID-19 pandemic, as part of the NHS England Osteogenesis Imperfecta National Service

Anita Freeman¹, Rebecca Jones²

¹Great Ormond Street Hospital, London, United Kingdom. ²Sheffield Children's Hospital, Sheffield, United Kingdom

ABSTRACT

BACKGROUND: The COVID-19 pandemic was an isolating experience for children and families, especially so for those classified as vulnerable¹ which included many in the Osteogenesis Imperfecta (OI) community.

PRESENTING PROBLEM: The pandemic meant that being together as a group was not possible, however young people have previously shared with psychology a sense of difference due to their OI and an importance of meeting other young people living life with OI. The psychologists involved recognised the significance of shared experiences with peers, the importance of group therapeutic spaces, and a need to provide this during the pandemic.

CLINICAL MANAGEMENT: We took the opportunity to work cross centre to use the successfully adapted Narrative Therapy Tree of Life young people group² in a video based setting. This allowed young people to meet virtually regardless of their location. The group ran during one full day during the school holidays facilitated by Clinical Psychologists from Great Ormond Street Hospital and Sheffield Children's Hospital. The group included breakout rooms and whole group work with a focus on developing a narrative of a young persons' experience of OI and integrating this into their identified personal strengths and interests, promoting resilience.

DISCUSSION: Feedback from young people indicated that they had gained personal insights and understanding through the narrative work as well as the opportunity to connect with other young people with OI. Based on feedback further collaborative groups are planned and these will involve a hybrid of online and in-person group sessions.

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P27

Cardiovascular characteristics and abnormalities in patients with Osteogenesis Imperfecta: a systematic review

Sara J.E. Verdonk^{1,2}, Silvia Storoni^{1,2}, Dimitra Micha³, Joost G. van den Aardweg⁴, Otto Kamp⁵, Marianna Bugiani⁶, E. Marelise W. Eekhoff¹

¹Amsterdam UMC Location Vrije Universiteit Amsterdam, Department of Internal Medicine Section Endocrinology, Amsterdam, Netherlands. ²Amsterdam Movement Sciences, Tissue Function and Regeneration, Amsterdam, Netherlands. ³Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Human Genetics, Amsterdam, Netherlands. ⁴Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Respiratory Medicine, Amsterdam, Netherlands. ⁵Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Cardiology, Amsterdam, Netherlands. ⁶Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Pathology, Amsterdam, Netherlands

ABSTRACT

OBJECTIVES: Osteogenesis imperfecta (OI) is a rare disease caused by a genetic defect that results in abnormal production of collagen type 1. Since collagen type 1 is the most abundant protein in the bone tissue, bone deformities and fractures are the most noticeable clinical manifestations in OI patients. Until now little attention has been focused on the effect of abnormal collagen type 1 on extraskeletal tissues, such as the heart and blood vessels. Collagen type 1 is found in blood vessel walls, heart valves and the myocardium. It is the most abundant protein in the extracellular matrix of the heart. Thus, OI defects in collagen type 1 can potentially affect heart structure and function. This systematic review aims to provide an overview of cardiovascular problems that may be associated with OI.

METHODS: PubMed, Embase and Scopus were searched for relevant publications from inception up to November 2021. Quality assessment was independently performed by two researchers on all included articles describing cardiovascular diseases/risk factors and OI. Studies published in English were included.

RESULTS: In total 3697 articles were identified of which 211 were included for full-text analysis. The studies included consisted of case-reports, case-series and case-control studies. Aneurysms and/or dissections have been reported in the literature in various blood vessels. Examples include aortic dissections and subdural hematomas due to ruptured cerebral blood vessels. In studies in which cardiac ultrasound was performed valvular insufficiency and aortic root dilatation were reported. Furthermore, patients with OI seem to be more at risk at having atrial fibrillation/flutter and heart failure.

CONCLUSION: Based on the pathophysiology, the effects of the OI mutation can also manifest in the heart, blood vessels and cerebrovascular system. Several articles have been published on these topics. However, real prospective studies have not yet been conducted. This is an urgent requirement considering the relatively high reported frequency of cardiovascular death in OI. More information about the cardiovascular pathology in OI is needed in order to investigate a possible causal relation.

P28

Molecular characterization of a newly reported MBTPS2 variant in a fetus affected with severe Osteogenesis Imperfecta

Giulio Marcionelli¹, Pei Jin Lim¹, Timothée Ndarugendamwo¹, Jason Pinner², Marianne Rohrbach¹, Cecilia Giunta¹

¹University Children's Hospital Zurich, Zurich, Switzerland. ²Sidney Children's Hospitals Network, Sydney, Australia

ABSTRACT

OBJECTIVES: We described the first X-linked recessive form of Osteogenesis imperfecta caused by MBTPS2 missense mutations in patients presenting with moderate to severe phenotypes. Missense mutations in MBTPS2 laying in proximity to those found in OI, cause

the dermatological condition IFAP/ KFSD without skeletal abnormalities. RNA-sequencing based transcriptomics analysis of MBTPS2-OI fibroblasts showed alterations in the expression of genes involved in lipid metabolism, cartilage and bone development (1). Furthermore, we showed a reduction in collagen deposition in the ECM by immunofluorescence analysis⁽¹⁾. A male proband terminated at gestational week 21/40 for severe skeletal dysplasia presented with shortening of all long bones and bowing of the femurs and tibiae. Post-delivery examination, radiology and autopsy confirmed the clinical diagnosis of OI. WES based brittle bone dysplasia panel identified a previously unreported c.516A>C; p.Glu172Asp variant in MBTPS2 classified as variant of uncertain significance. Functional studies have been undertaken to infer pathogenicity of this variant.

METHODS: Total RNA was extracted from cultured fibroblasts of the aborted MBTPS2-OI fetus, an aborted COL1A2(Gly553Asp)-OI fetus and two previously characterized MBTPS2(Leu505Phe)-OI and IFAP/KFSD patients. Gene expression changes of FADS1, DHCR24, CHST3, VEGFA, ADAMTS12, DKK1 and COL1A1 showing differential expression in MBTPS2-OI were measured by RT-qPCR. Immunofluorescence staining was performed to investigate extracellular matrix protein deposition by fibroblasts in culture. Furthermore, lipids extracted from cultured fibroblasts were measured by GC-MS/MS.

RESULTS: In the fibroblasts of the MBTPS2-OI aborted fetus we observed: i) changes in the expression of the selected genes involved in lipid metabolism (FADS1 and DHCR24), coupled with changes in the relative ratios of cellular fatty acids, as well as genes involved in skeletal/cartilage/bone development (CHST3, VEGFA, ADAMTS12, COL1A1 and DKK1); ii) a reduction in collagen deposition in the ECM by immunofluorescence staining. These alterations were similar to those documented in MBTPS2-OI patients (1).

CONCLUSIONS: These findings support pathogenicity of the newly identified MBTPS2 p.Glu172Asp as an OI causing variant, without overlap at the molecular level with IFAP/KFSD caused by MBTPS2 variants. This study shows the value of implementing datasets identified in a multi omics study to molecularly characterize a genetic variant of unknown significance.

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1 doi: 10.3389/fgene.2021.662751.

P29

Studies of OI Patient and Murine Osteoblasts to Investigate Phenotypic Variability of Dominant Osteogenesis Imperfecta

Milena Jovanovic¹, Apratim Mitra¹, Chris Stephan², Kenneth Kozloff², Ryan Dale¹, Joan Marini¹

¹NICHD/NIH, Bethesda, USA. ²University of Michigan, Ann Arbor, USA

ABSTRACT

OBJECTIVES: An important and unexplained feature of Osteogenesis Imperfecta (OI) is phenotypic variability among individuals with the same mutation. We present the first comparative study of osteoblasts from normal pediatric controls vs OI patients with phenotypic variability. Additionally, we study phenotypic variability in OI-mouse models comparing a new Brlt(Ser)(G349S) mouse to Brlt(Cys)(G349C).

METHODS: Osteoblast differentiation, steady-state collagen, amino-acid analysis, RNA-Seq, SUNSET, Western blot, immunocytochemistry, electron microscopy, µCT, skeletal staining.

RESULTS: We studied COL1A1 substitutions G352S and G589S, each expressed in two unrelated patients differing in phenotypic severity. Patient osteoblast intracellular and secreted collagen were overmodified, however collagen hydroxylysines were not different within pairs. Severe patients' osteoblasts deposited significantly less mineral than mild patients; all patients deposited less than controls. RNA-Seq of patients' differentiated osteoblasts showed upregulated proteasomal protein degradation, autophagy, and vesicle organization vs controls, while protein translation was downregulated. Puromycin treatment showed osteoblast protein synthesis was significantly upregulated in severe vs

mild patients in both pairs. UPR PERK pathway and ER chaperones were affected differently between pairs. PERK and BiP were increased in mild G589S osteoblasts, while calnexin and PDI increased in severe G589S osteoblasts. Contrary, mild G352S osteoblasts had decreased PERK and all chaperones were decreased in G352S patients. Correspondingly, autophagy marker Beclin was increased only in mild G352S osteoblasts. CHOP was increased in all patient osteoblasts without phenotypic correlation. Downstream of CHOP, ERO1La, which oxidizes PDI, increased early in osteoblast differentiation. Patient osteoblasts EMs showed unexpectedly thin, very elongated mitochondria with cristae dropout.

Additionally, we studied phenotypic variability comparing Brlt(Ser) and Brlt(Cys) mice. Brlt(Ser) has a more severe phenotype with rib fractures, limb bowing, flared ribcage, kyphosis. Preliminary µCT data indicated severely decreased trabecular BV/TV (13% of WT) and cortical CSA (47% of WT) in Brlt(Ser) 7-wk-femora. Brlt(Ser) calvarial osteoblasts have ~1/3 collagen secretion, ~2/3 mineral deposition, and condensed actin by phalloidin staining vs WT. Brlt(Ser) dermal collagen fibrils have tighter packing and smaller cross-section.

CONCLUSIONS: This combined study leads to novel insights highlighting osteoblast differentiation, mineralization, and potential role of mitochondria in OI pathology and phenotypic variability, together with individual ER stress and chaperones differences.

P30

A new X-linked PLS3 gene variant identified in a patient with osteogenesis imperfecta

Petar Brlek^{1,2}, Darko Antičević^{1,3}, Vilim Molnar¹, Vid Matišić¹, Andrea Skelin¹, Kristina Robinson⁴, Swaroop Aradhya⁴, Dalibor Krpan⁵, Dragan Primorac^{1,3,6,7,8,9,10,11,12}

¹St. Catherine Specialty Hospital, Zagreb, Croatia. ²Laboratory of Neurooncology, Croatian Institute for Brain Research, Zagreb, Croatia. ³Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia. ⁴Invitae, San Francisco, USA. ⁵Polyclinic "K-Center", Zagreb, Croatia. ⁶Department of Biochemistry & Molecular Biology, The Pennsylvania State University, University Park, USA. ⁷The Henry C. Lee College of Criminal Justice and Forensic Sciences, University of New Haven, West Haven, USA. ⁸Medical School, University of Split, Split, Croatia. ⁹School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia. ¹⁰Medical School, University of Rijeka, Rijeka, Croatia. ¹¹Medical School REGIOMED, Coburg, Germany. ¹²Medical School, University of Mostar, Mostar, Bosnia and Herzegovina

ABSTRACT

BACKGROUND: Traditional types of osteogenesis imperfecta (OI) (types I-IV) are inherited in an autosomal dominant manner and encompass about 80–85% of OI cases caused by pathogenic variants of genes essential for normal extracellular matrix (ECM) function. In recent years, technological advances in molecular medicine uncovered more than 24 different genes involved in pathophysiology of OI.

PRESENTING PROBLEM: We present a case of a rare X-linked OI with a change in the gene encoding for plastin 3 involved in intracellular calcium PLS3-dependent processes. A 16-year-old proband, who complained of pain, pathological fractures, and patellar subluxations that arose due to a moderate valgus of the distal femur, was admitted to St. Catherine's Specialty Hospital. He suffered his first low-trauma fracture at the age of 2. Since then, he had experienced a total of 10 fractures, including a compression fracture of the L2 vertebra. He had low bone mineral density (BDM) at the lumbar spine and left hip. The proband's mother and 14-year-old sister were healthy with normal hearing, sclerae, dentition, joint laxity, and without a history of bone fractures. Their BDMs indicated initial osteoporotic changes. The proband's father and his parents were healthy with no history of fractures.

CLINICAL MANAGEMENT: Genomic DNA was isolated from the blood samples and subjected to clinical next-generation sequencing using a multi-gene panel that included 320 genes. We identified a c.685G>A (p.Gly229Arg) variant in the X-linked PLS3 gene in the patient, his mother, and sister.

DISCUSSION: Since the *PLS3* gene is located on the X chromosome, the heterozygous mother and sister showed no signs of the disease. Although the variant has not yet been described in the literature, nor is its pathogenicity known, clinical findings combined with genetic testing showed that this variant explained the cause of our patient's disease. Further studies on the molecular substrate involved in the regulation of signaling pathways that control bone remodeling are needed to improve the treatment of patients with bone dysplasia. Future research on the role of *platin 3* in the process of bone remodeling regulation by osteoblasts and osteoclasts will shed light on potential molecular targets in personalized therapy.

P31

Genotype-phenotype correlation and effects of bisphosphonates in rare forms of osteogenesis imperfecta: a retrospective study

Maelle Charpie¹, Perrine Brunelle¹, Geneviève Baujat¹, Caroline Michot¹, Julien Van Gils², Bruno Leheup³, Elise Schaefer⁴, Zagorka Pejcin¹, Graziella Pinto¹, Sophie Monnot¹, Valérie Cormier-Daire¹

¹Hôpital Necker-Enfants Malades, Paris, France. ²Centre Hospitalo-Universitaire de Bordeaux, Bordeaux, France. ³Centre Hospitalo-Universitaire de Nancy, Nancy, France. ⁴Institut de Génétique Médicale d'Alsace, Strasbourg, France

ABSTRACT

Osteogenesis Imperfecta (OI) is a heterogeneous group of diseases characterized by brittle bones causing fractures for minor trauma. Genetic mutations in *COL1A1* and *COL1A2* account for approximately 85-90% of OI cases. More recently, new forms of OI have been discovered with currently more than twenty genes described. Treatment is based on the wide use of bisphosphonates and though it is well established that they increase lumbar spine (LS) bone mineral density (BMD), the clinical impact on fracture reduction is still debated.

In this study, we first investigated the clinical characteristics of 40 patients with variants in genes other than *COL1A1/COL1A2* in order to study genotype-phenotype correlations as the natural history of these rare forms is still little known. We then studied the usefulness of bisphosphonate treatment by evaluating the effects on LS BMD, annual non-vertebral fracture rate, and height.

This retrospective cohort study included 21 men and 19 women with an average age of 12.3 years. The main genes involved were *IFITM5* (n=10), *FKBP10* (n=7), *SERPINF1* (n=6), *CRATP* (n=5), *LEPRE1* (n=3), *CCDC134* (n=3), *PLS3* (n=2), *TMEM38B* (n=2) and *SERPINH1* (n=2). Clinical characteristics as well as LS BMD and history of fractures were collected for these patients.

This study allowed us to further define two phenotypes. Indeed, patients with *CRTAP* variants had an antenatal presentation with a short (<3rd p) and curved femur. They can also present with more moderate forms, further extending the phenotypic spectrum of OI forms linked to *CRTAP*.

In patients with *SERPINF1* variants, we consistently observed progressive deformities and loss of mobility.

Regarding treatment by bisphosphonates, all patients showed a significant increase in LS BMD while treated and this increase was dependent on the dose received. The increase in LS BMD also translated in a reduction of fracture rate during treatment. Finally, our study showed that the earlier bisphosphonates are initiated, the greater the fracture rate is reduced.

P32

Pulmonary Complications in Osteogenesis Imperfecta Type III

Hollis Chaney

Children's National Hospital, Washington, DC, USA

ABSTRACT

BACKGROUND: 32-year-old woman who had multiple pulmonary complications secondary to OI

PRESENTING PROBLEM: As a child: multiple surgeries for fractures

Ages 8 and up: Severe constipation resulting in multiple hospitalizations. She had frequent and recurring reflux-triggered aspiration pneumonia and asthma.

Teenager: severe scoliosis (thoracic: 107 degrees; lumbar: 78 degrees) causing severe lung restriction (34% of normal capacity). Survival from scoliosis surgery was predicted as only 50% which led to severe anxiety.

The patient was admitted every 2 weeks with ongoing constipation, gastroesophageal reflux, asthma, recurrent pneumonia, chronic inflammation, and infection. Her severe anxiety continued as well.

A sleep study confirmed hypoventilation with inability to oxygenate or remove carbon dioxide. Treated with BiPAP (Bilevel Positive Airway Pressure).

Age 22: pregnancy resulting in need for almost full time BiPAP and high levels of oxygen; admitted six times between 22-27 weeks gestation for respiratory distress; C section at 28 weeks; infant 2 pounds 2 ounces.

CLINICAL MANAGEMENT: Treatment was directed at her individual problems of constipation, reflux, pneumonias, asthma, anxiety, and sleep. Lessons learned are included under discussion below.

DISCUSSION: There are multiple potential complications related to the lungs in OI that should be monitored closely and treated aggressively

1. Treat constipation early. For example, opioids after surgery commonly lead to constipation. Constipation restricts diaphragm movement and lung expansion. It is also associated with reflux.
2. Gastroesophageal reflux: aggravates asthma, leads to aspiration and recurrent pneumonia. Small frequent meals, limit eating before bedtime, acid suppression and avoid constipation.
3. Aspiration pneumonias: Aggressive airway clearance including cough assist, mucolytic agents, early use of antibiotics, use of inhaled steroids and limited use of oral steroids.
4. Scoliosis: restricts size of lungs, compromises airway clearance. Monitor when young including pulmonary function. Surgery before recurrent pneumonia or severely abnormal lung function
5. Ineffective breathing: While sleeping BiPAP prevents low oxygen and high carbon dioxide. May need positive pressure while awake when sick or pregnant: can be intermittent positive pressure, BiPAP, or cough assist.

This case illustrates the crucial need for careful monitoring and active management of pulmonary status in OI.

P33

Port-a-Cath Placement in Pediatric Patients with Osteogenesis Imperfecta Requiring Long-Term Vascular Access

Andrew White¹, Jay Byrd¹, Makayla Schissel¹, Vincent Eaton², Kaeli Samson¹, Elizabeth Strudthoff¹, Maegen Wallace¹

¹University of Nebraska Medical Center, Omaha, USA. ²Creighton University, Omaha, USA

ABSTRACT

OBJECTIVES: IV bisphosphonate therapy decreases fracture rate while increasing bone density in OI patients. IV access in OI patients can be traumatic and cause fractures. This may be mitigated with port-a-cath placement, minimal investigation of port placement in OI patients exists. This study investigates outcomes and identifies potential morbidities due to port-a-cath placement.

METHODS: We performed a retrospective review of 58 port-a-cath placements in 31 patients with OI from 2000-2021. Variables collected included demographic data, OI type, weight at placement, port location, port longevity, number of placements, complications with access, and replacements. Spearman correlation coefficient was used to assess the potential relationship between age and number of port placements in individuals. Wilcoxon Rank Sum tests were performed to evaluate differences between number of port placements and gender or OI type. Port longevity was compared between gender, OI type, and placement location. OI types with less than 5 individuals (I and V) were excluded.

RESULTS: Of the 31 individuals, most are OI type III (58.06%), followed by IV (19.35%), I (12.90%), and V (9.68%). 29% female, and 71% male. 32% of individuals had 1 placement, 52% had 2, 13% had 3, and 3% had 4. Port removal was due to malfunction (71.43%), infection (4.76%), or misposition (4.76%), and 19.05% were removed for unknown reasons. Median port longevity was 43.7 months, with no significant difference in longevity and gender, OI type, or port location. We found a significant positive correlation between the number of placements and age ($R=0.75$, $p<0.0001$), suggesting that number of ports increases with age. There is a significant difference ($p=0.005$) between the number of placements and OI type, with type IV having more than type III.

CONCLUSION: We found that patients who require a port generally require replacement due to malfunction, conflicting with another study that reported 67% of removals were because the port was no longer needed. Interestingly, those with more severe OI type III required fewer replacements than those with type IV. Complications associated with port placement are mild, suggesting the efficacy of port use in this population. Further investigation is needed to identify factors that may predict placement longevity or potential complications.

P34

Intramedullary canal sclerosis as a result of prolonged bisphosphonate therapy in children with osteogenesis imperfecta type III and IV

Željko Jeleč^{1,2}, Dragan Primorac^{1,3,4,5,6}, Darko Antičević^{1,5}

¹St. Catherine Specialty Hospital, Zagreb, Croatia. ²University North, Varaždin, Croatia. ³The Pennsylvania State University, State College, USA. ⁴University of New Haven, West Haven, USA. ⁵University "J.J.Strossmayer", Osijek, Croatia.

⁶University of Split, Split, Croatia

ABSTRACT

OBJECTIVES: Conservative approach with the bisphosphonate (BP) intravenous infusions is a cornerstone of the treatment of osteogenesis imperfecta (OI). The main goal of our study was to show the changes in long bone morphology which were connected with prolonged BP administration before the surgery. The emphasis was on intramedullary sclerosis, which hasn't been described in literature yet. We also wanted to show difficulties in surgical treatment and present our techniques in solving these problems.

METHODS: The main inclusion criterium for this study were patients without previous surgery. Other inclusion criteria were severe deformation of long bone segment (more than 50 degree of varus or procurvatum) and prolonged treatment with BP before the surgery. All radiographs were reviewed by single reviewer (orthopaedic surgeon). Because most of segments were severe deformed and had a specific "rib shape", analysis was possible in lateral radiographs only. Our reviewer determined the start and the end points of sclerosing area and, according that, measured and calculated a whole surface of sclerosing and percent of sclerosing part in measured area. An angles of varus and procurvatum were measured also. The whole procedure was repeated three times, and final results was an arithmetic mean value.

RESULTS: We found 17 segments (14 femurs and 3 tibias) in 9 patients which had intramedullary sclerosis, most often on the apex of the deformity. All of included children were treated with intravenous infusions of pamidronate. Main difficulties during surgery (implanting Fassier-Duval rod) are splintering of the bone, drill breakage, "false route", bone necrosis, malposition of the implant, prolonged duration of the surgery and increased blood loss. Our suggestions how to avoid surgical difficulties are: precise preoperative planning, precise operative technique, many x-ray controls, gradual and patient reaming, reaming with surgical drill (instead of cannulated drill) and excision of the bone block (triangular or trapezoidal shape).

CONCLUSION: The correct way of treatment of OI is to start with BP first. However, it is necessary to decide when to interrupt the conservative and start with the surgical treatment. According to our results, the threshold for the operative treatment should be fifteen cycles of BP infusions.

P35

Tibial Rodding Challenges and Nailing Technique Choice in Children with Osteogenesis Imperfecta and Narrow Intramedullary Canals Using the "Telescoping Principles": A Narrative Review and Expert Opinion

Alice Tao Ran Guo¹, Argerie Tsimicalis^{1,2}, Reggie Hamdy^{1,2}

¹McGill University, Montreal (QC), Canada. ²Shriners Hospital for Children, Montreal (QC), Canada

ABSTRACT

Objectives. Osteogenesis imperfecta (OI) is a genetic disorder causing collagen anomalies in connective tissues including bones. In OI children, intramedullary nailing helps correct lower-limb deformities and stabilize fractures during growth. Surgical stabilization early in life improves verticalization, walking and motor skill acquisition by minimizing fractures and immobilization. Telescopic (Sheffield or Fassier-Duval) rods are currently preferred, but they can be unsuitable for children with narrow medullary canals due to the implants' larger diameter. Surgical approach for these children is poorly reported in the literature. This narrative review seeks to study the challenges with tibial intramedullary rodding in children ineligible for telescopic rods and understand alternatives that follow "telescoping principles".

Methods. The MEDLINE database was searched via PubMed. Included articles were peer-reviewed, in English, published or referenced in the last five years, with OI pediatric patients who underwent a non-telescopic intramedullary nailing surgery. Surgical techniques were studied with attention to indications, outcomes, and complications.

Results. Only one study was found: it showed that sliding elastic nailing corrects angular deformations well, yielding satisfactory long-term clinical and radiological results for 22 OI children receiving 38 operations. The mechanical complication rate was 42%; the revision rate of 55% was comparable to 46% for Fassier-Duval nails. Sliding elastic nailing is minimally invasive, simpler and less costly. In fact, using plates and screws alone is not recommended, and using a single static device requires more surgical revisions due to bone growth unaccompanied by rod elongation. Using telescopic rods is ideal, but very young children are often ineligible. The sliding rod technique addresses this problem by mimicking the telescoping effect using two static nails, one inserted antegrade, one retrograde. With bone growth, those nails slide similarly to telescopic rods. The use of this sliding technique in OI is however poorly reported.

Conclusions. Delaying surgery should be avoided to improve verticalization, walking, motor skill acquisition, and prevention of secondary osteoporosis. For children ineligible for telescopic rods because of narrow tibial medullary canals, sliding elastic nailing can be a viable alternative. However, further studies with a greater sample size, ideally multicenter, are needed to validate the technique, indications and outcomes.

P36

Bone microarchitecture in osteogenesis imperfecta assessed with high-resolution peripheral quantitative CT

Melissa Bevers^{1,2,3}, Arjan Harsevoort⁴, Daniëlle Bout⁴, Caroline Wyers^{1,2}, Bert van Rietbergen³, Joop van den Bergh^{1,2}, Guus Janus⁴

¹VieCuri Medical Center, Venlo, Netherlands. ²Maastricht University Medical Center, Maastricht, Netherlands. ³Eindhoven University of Technology, Eindhoven, Netherlands. ⁴Isala Hospital, Zwolle, Netherlands

ABSTRACT

OBJECTIVES: Dual-energy X-ray absorptiometry (DXA) is generally used to assess areal bone mineral density (BMD) and fracture risk in patients with osteogenesis imperfecta (OI) but may not completely reflect bone fragility in OI. High-resolution peripheral quantitative CT (HR-pQCT) allows detailed assessment of bone microarchitecture and strength. Using HR-pQCT, we evaluated volumetric BMD,

microarchitecture, and failure load (FL) in adult OI-patients as compared to normative data.

METHODS: HR-pQCT scans were acquired of the non-dominant distal radius and tibia of 57 OI-patients aged ≥ 18 years using a length-dependent protocol. In case of a recent fracture (< 2 years) or metal implant, the dominant side was scanned. Volumetric BMD, microarchitecture, and FL were quantified from the scans; Z-scores were determined using a normative dataset.1

RESULTS: The patients (28 men, 29 women; 41.2 (IQR: 27.6) years old) had Sillence OI type I (44, 77%), III (4, 7%), or IV (9, 16%) with a median of 17 (IQR: 27) self-reported fractures. Areal BMD Z-score was < -1.0 in 44% at the total hip and in 72% at the lumbar spine. Acceptable HR-pQCT scans were acquired at the radius in 49 patients (86%) and at the tibia in 53 patients (93%). From these scans, Z-scores at the radius were < -1.0 for total BMD in 47% (type-I: 20, type-III: 1, type-IV: 2 patients) and for trabecular BMD in 76% (type-I: 33, type-III: 1, type-IV: 3 patients). Correspondingly, trabecular number and separation Z-scores were < -1.0 in the majority of patients (86% and 84%, respectively). Cortical BMD Z-score was < -1.0 in only 18%. A similar pattern with larger proportions was found at the tibia with additionally a large proportion of low cortical area. Finally, FL Z-score was < -1.0 at the radius in 51% (type-I: 23, type-III: 1, type-IV: 1 patients) and < -2.0 at the tibia in a similar proportion (53%).

CONCLUSION: These preliminary results show that especially the trabecular compartment at the distal radius and tibia may be deteriorated in OI-patients compared to age- and gender-matched controls, with a more pronounced impairment at the tibia. We aim to include more OI-patients for further study.

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P37

Early intervention program for children with OI. 5 years of experience of the Center for Inborn Pathology GMS Clinic

Natalia Belova, Inna Passechnik, Daria Ivanchenko, Tatiana Khasianova
GMS Clinic, Moscow, Russian Federation

ABSTRACT

BACKGROUND: OI mainly affects the connective tissue and results in multiple fractures and skeletal deformities. Normally the intellectual development of children with OI is not affected, with the exception of some rare forms (e.g. TMEM 38B and WNT). Specific life conditions of children with OI related to deprivation and decreased motor activity can lead to impaired cognitive development.

PRESENTING PROBLEM: Cognitive development and parent-child relationship has been examined in patients of the Centre of Inborn Pathology since 2017. In 282 patients aged 4 - 18 years the following problems were identified: speech disorders (25% of children under 7 years, 44% of children 7-11 years), thinking processes and attention problems in 97% of all children. Socialization, independence and self-care also has been suffered. Parent-Child interaction was characterized by the following problems: parental fears, deprivation, hyperprotection, "magical" thinking. An early intervention program was designed for patients born in 2017 and later, who were admitted for treatment before the age of 3 years.

The early intervention program was based on the main problems identified during the examination of 282 patients and their parents. Along with the comprehensive treatment of OI, all children and parents were examined and counseled by a psychologist and a special education teacher.

The majority of the patients (270 children) were referred to the Center older than 3 years old, when the consequences of deprivation, limitation of motor activity, parenting practices had been already formed. Only 12 children were observed from birth and were evaluated in comparison to the main group.

A support program for children from birth to age 5 included 4-6 visits per year to improve conditions for children's mental development and to create a developmental environment.

Discussion. Social isolation, anxiety, and hyperprotection by primary caregiver inhibit children's mental development, self-care skills, and socialization. Despite the fact that the nervous system of most patients with OI is not affected, an early intervention program is necessary for the successful rehabilitation and treatment of these patients.

P38

Stiff hips in patients with Osteogenesis Imperfecta: a providential femoral neck fracture

Marine De Tienda, Mathilde Gaume, Tristan Langlais, Georges Finidori, Zagorka Pejcin
Necker Hospital, Paris, France

ABSTRACT

OBJECTIVES: Osteogenesis Imperfecta (OI) is characterized by fragile and deformed bones which may manifest by severe acetabular protrusion. Accordingly, hips become stiff, painful and unfunctional. In these patients, femoral neck fractures are difficult to manage as require coxa vara correction with an adapted osteosynthesis. Looking for bone consolidation is illogical as stiffness may be perpetuated and the main risk of the surgery is pseudoarthrosis. The aim of this study was to assess clinical outcomes after functional treatment and voluntary pseudoarthrosis.

METHODS: A retrospective evaluation allowed to determine functional discomfort such as inability to sit and irreducible adduction thanks to the Harris Hip Score (HHS). The protrusion was measured on an anteroposterior radiograph as the distance between the acetabular line and the laterally located ilioischial line and the Wiberg angle. Functional management of the fracture consisted in verticalization without support and early mobilizations.

RESULTS: 15 hips in 12 patients including 8 women were reported with a mean follow-up of 5 years. The mean age was 22. Two pseudoarthrosis were surgically induced in the face of painful ankylosis. Mean Wiberg angle was 42 degrees and medial distance was 20mm. Mean HHS was 59/100 before fracture. It was increased to 67/100 at last follow-up. Mean range of motion in abduction was increased from 15° to 30° and in flexion from 45° to 90°. In the early follow up, 2 patients suffered from very intense pain that resolved after 3 months. At last follow-up, in patients with surgical pseudoarthrosis one kept an unstable limp and the other suffered from chronic pain treated with simple pain killers.

CONCLUSION: In patients with OI and stiff hips, pseudoarthrosis seems to be a reasonable femoral neck fracture treatment enabling functional improvement. The results of surgical fractures appear more random.

P39

Tibia sliding elastic nailing technique in moderate-to-severe Osteogenesis Imperfecta: long-term outcomes

Mathilde Gaume, Eloise Duprot, Marine De Tienda, Georges Finidori, Zagorka Pejcin, Tristan Langlais
Necker Hospital, Paris, France

ABSTRACT

OBJECTIVES: Osteosynthesis of leg fractures and deformities in children with osteogenesis imperfecta should align the skeleton and overcome its fragility during growth. The objective was to assess long-term outcomes of Tibial Sliding Elastic Nailing technique (T-SEN).

METHODS: 22 children with an average age of 4.7 years were operated unilaterally (6) or bilaterally (16). They were listed according to Sillence classification into type I (3), III (17), V (2). The nails were introduced percutaneously at the distal tibial epiphysis through the medial malleolus, and in the pre-spinal area for the proximal tibial epiphysis. Correction of the deformation and the width at mid-shaft of the tibia in

frontal and sagittal planes were reported on X-rays. Gillette's functional score, pain, mechanical and infectious complications were collected.

RESULTS: Average follow-up was 8.6years. In the frontal plane, preoperative average varus was 8° (max 40°), 5° (max 13°) postoperatively and 6° (max 12°) at last follow-up. Preoperative valgus was 11° (max 22°), 9° (max 15°) postoperatively and 9° (max 14°) at last follow-up. Mean sagittal bowling of the tibia was 32° (4-75°) preoperatively, 9° (1-26°) postoperatively and 9° (1-24°) at last follow-up. Width at mid-shaft of the tibia in the frontal plane was 1.1cm (0.6-1.8cm) preoperatively and 1.3cm at last follow-up (0.7-2.0cm). In the sagittal plane, it was 1.25cm (0.7-2.7cm) preoperatively and 1.27cm (0.8-2.8cm) at last follow-up. 10 patients didn't require revision surgery. 16 mechanical complications occurred in 12 patients (12 fractures or deformities, 3 prominence of the nail, 1 pseudarthrosis). Gillette's functional score was 20.54 / 65. Fifteen patients were able to walk and 18 had no pain at last follow-up.

CONCLUSION: T-SEN technique provides satisfactory clinical and radiological results over time. Performed in case of fracture or as a preventive treatment, it allows a good correction of angular deformations.

P40

Laboratory assessment in patients with the highest bleeding scores on the Self bleeding assessment tool out of 195 patients with Osteogenesis Imperfecta

Koert Gooijer^{1,2}, Gabriëla Heidsieck¹, Arjan Harsevoort¹, Guus Janus¹, J.J.C.M van der Leur³, Jan Rondeel³, Anton Franken¹

¹Expert Center for adults with Osteogenesis Imperfecta Isala Hospital, Zwolle, Netherlands. ²Department of Clinical Genetics, Amsterdam Reproductive & Development research institute, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands. ³Department of Clinical Chemistry, Isala, Zwolle, Netherlands

ABSTRACT

BACKGROUND: Osteogenesis Imperfecta (OI) is characterised by bone fragility. Among several features, easy bruising and multiple case reports on haemorrhagic events without consistent clarification has been reported. Recently we described the clinical aspects of bleeding in a large cohort of adult OI patients. The aim of this study is to find in the same cohort consistent explanatory coagulation disorders in laboratory analysis in patients with a high bleeding score compared to patients with a normal bleeding score using the Self-BAT tool.

METHODS: This study was conducted at the National Expert Center for adults with OI in the Netherlands. The Self-BAT was administered among 354 OI patients and 195 patients completed the tool. From the highest bleeding scores 11 patients were included. A random selection of 9 patients with a normal bleeding score were included for comparison. Routine coagulation testing consisted haematocrit, platelet count, activated partial thromboplastin time (APTT), fibrinogen, FVIII activity and von Willebrand factor (VWF) antigen and activity. Additionally bleedingtime, platelet function and thromboelastometry (ROTEM) was performed.

RESULTS: Bleeding time according the Ivy method was prolonged in 2 out of 20 patients. Routine coagulation analysis comprising full blood count, analysis showed a single patient with lower fibrinogen level, and 3 patients with abnormal Factor VIII or Von Willebrand factors. Platelet function measured with the PFA-200 resulted in 6/20 (30%) deviating values. All ROTEM results were inconclusive.

CONCLUSION: An underlying mechanism for the reported bleeding problems among OI patients could not be identified. The results are diverse and do not point in an unambiguous direction. It might be considered to monitor PFA-200 results on larger scale, possibly extended with platelet aggregation tests.

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Understanding the Physical Well-being of Adults with Osteogenesis Imperfecta

Kathleen Montpetit¹, Marjolein Verhoef², Wenche Wilhelmsen³, Lena Lande Wekre⁴

¹Shriners Hospital for Children, Montreal, Canada. ²Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, Netherlands. ³TRS National Resource Center for Rare Disorders, Sunnaas Rehabilitation Hospital, Oslo, Norway. ⁴TRS National Resource Center for Rare Disorders, Sunnaas Rehabilitation Hospital, Oslo, Norway

ABSTRACT

BACKGROUND AND OBJECTIVE: In 2020 the World Health Organization (WHO) formulated guidelines on physical activity, an important aspect of one's physical well-being. To understand the needs of adults with OI regarding physical activity (active living, sport, fitness and exercise) we decided to explore this further.

METHODOLOGY: A survey on physical well-being and OI was developed by a subcommittee of the Care4Brittle Bones Foundation; three health care professionals and a representative from the OI community. The survey was available for completion from May 12th to June 26th, 2021 and distributed through several social media platforms.

PRELIMINARY RESULTS: Two hundred and seventy-three persons with OI responded and provided important insights into their experience with, and feelings about, physical activity. The respondents were mainly female (72%) aged 16 to 65+ years with an overall high level of independence in self-care. Their usual level of mobility was independent walking and one third used a wheelchair.

Half of the respondents participated in exercise or sports on a weekly basis at low to moderate intensity. More than half was less active than previously. Factors helping to be physically active were (customized) exercise programs, knowledge of local facilities and access to equipment or assistance.

They described succinctly the health benefits of an active lifestyle. Challenges faced when active were pain management, cost and fear of fractures.

Sleep issues were present in 25% of respondents and 40% were often or always feeling tired during the day.

CONCLUSION: Although people with OI encounter challenges in being physically active, many of them succeed. However more than half of the respondents stated to be less active than previously. Further analysis of motivating factors, challenges, knowledge of sleep issues, and nutrition is necessary to support people with OI to be physically active.

The ultimate goal is to use the feedback from this survey to develop guidelines and material in accordance with WHO's recommendations for physical activity and adapted to people with OI. These "tool kits" should be developed in collaboration with professionals, training experts and the OI community using a broad perspective on physical wellbeing.

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Treatment response in Osteogenesis Imperfecta - two-year retrospective analysis of paediatric patients treated with bisphosphonates

Mirko Rehberg¹, Sofie Menzel¹, Eckhard Schönau^{1,2}, Heike-Katharina Hoyer-Kuhn¹, Alice Stephan¹, Oliver Semler^{1,2}

¹Department of Pediatrics, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. ²Center of Prevention and Rehabilitation, UniReha, Faculty of Medicine and University Hospital, University of Cologne, Cologne, Germany

ABSTRACT

OBJECTIVES: Intravenous bisphosphonate treatment is the standard of medical care in severely affected children and adolescents with

Osteogenesis imperfecta (OI). The effect of bisphosphonates on pain, vertebral body shape and even mobility is well described in different cohorts and also subject of high quality reviews. Data of a comprehensive investigation of clinical, radiological and mobility response to bisphosphonate treatment in single, larger cohort is still missing, to define functional response/non-response criteria.

METHODS: We established a single center data base of more than 450 genetically confirmed individuals with OI, who were followed in our center between 01/2000 and 06/2021. Longitudinal data of those individuals were collected including audiology, areal bone mineral density of total body less head (TBLH-aBMD) and lumbar spine (LS-aBMD) measured by DXA corrected for age and height, standardized assessment of spine morphology and mobility tests (Gross Motor Function Measure (GMFM-88), Brief Assessment of Motor Function (BAMF), 1- and 6-minute walking test). For this analysis we extracted only data of patients complying the following criteria: Genetical mutation in COL1A1/2; clinical type 3 or 4; treated with iv bisphosphonates regularly for at least 2 years; visits before, during and after 2 years of treatment.

RESULTS: We present data of 92 patients with a median age at treatment initiation of 4.7 years (min: 0.0; max: 16.1). In 28 of those patients treatment was initiated in the first year of life. Height standard deviation score (SDS) was -4.2. TBLH-aBMD corrected for age increased from -2.65 ± 1.3 SDS to -2.2 ± 1.4 SDS and 1.66 ± 1.25 SDS after 1 and 2 years of treatment. LS-aBMD corrected for age showed an even more pronounced effect increasing from -3.96 ± 1.83 SDS to -2.8 ± 1.41 and to 2.37 ± 1.72 SDS respectively. Severity Score of spine morphology increased from median 28.11 to 26.16 and 18.11 after 1 and 2 years of treatment. GMFM-88 didn't change significantly.

CONCLUSION: 2 years of intravenous bisphosphonate treatment improves clinical and radiological parameters in paediatric patients with OI, while maintaining mobility level. Sub-group analysis and correlation to mobility of this cohort will be performed to propose functional response and non-response criteria.

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Relative larger Aortic Root Diameter in Osteogenesis Imperfecta Type 3 compared to type 1 and 4

A.M. Hupkes¹, K. Gooijer¹, J.P. Ottervanger², G.J. Harsevoort¹, M.A. Edens³, G.J.M. Janus¹, A.A.M. Franken¹

¹Expert Center for adults with Osteogenesis Imperfecta Isala, Zwolle, Netherlands. ²Department of Cardiology, Isala, Zwolle, Netherlands.

³Department Innovation and Science, Isala, Zwolle, Netherlands

ABSTRACT

OBJECTIVES: Aortic root dilatation is the most common cardiovascular abnormality in osteogenesis imperfecta (OI). However, it is still unclear whether the different types of OI have an association with aortic diameter. The aim of this study was to compare aortic root diameters in different types of OI in a large cohort of adult patients with OI.

METHODS: This retrospective, echocardiographic study was conducted at the national expert center for adults with OI in The Netherlands. Out of 379 consecutive adults with OI, 316 (i.e. 83.4%) patients, divided into 3 types (1, 3 and 4), were included. For the entire cohort, aortic root diameters adjusted for body surface area (BSA) were measured at the sinuses of Valsalva by transthoracic echocardiography.

RESULTS: In 316 adult patients with different types of OI (231/379 type 1, 30/379 type 3 and 55/379 type 4), aortic root diameter ranged from 22 to 44 mm (mean 31.3 mm). Patients with OI type 3 had significant larger aortic root diameter corrected for BSA (24.8 ± 4.7 mm/m²) compared to patients with OI type 1 (18.2 ± 2.6 mm/m² ($p < .001$)) and type 4 (18.7 ± 3.1 mm/m² ($p < .001$)). Additional analysis for independent associations were performed.

CONCLUSION: Aortic root diameter corrected for BSA is larger in patients with OI type 3 compared to OI type 1 or 4.

P44

Tooth size in individuals with osteogenesis imperfecta

Henri Tuurala¹, Heidi Arponen¹, Pyry Halonen², Janna Waltimo-Sirén^{1,3}

¹Department of Oral and Maxillofacial Diseases, University of Helsinki, Helsinki, Finland. ²The Department of Mathematics and Statistics, Helsinki, Finland. ³Institute of Dentistry, University of Turku, Turku, Finland

ABSTRACT

OBJECTIVES: The aim of this study was to assess whether the presence versus absence of clinical dental abnormality (dentinogenesis imperfecta, DI) in individuals with osteogenesis imperfecta (OI) affects the size of teeth. Our hypothesis was that the presence of DI reduces tooth size.

METHODS: The study was performed on dental plaster casts of 37 individuals with OI, of whom 11 were males and 26 were females. The subjects' ages ranged from 9.7 years to 74.7 years, median 31.86 years. In total, 16 individuals had type I OI (10 displaying DI), six had type III OI (2 displaying DI), and 15 had type IV OI (4 also displaying DI). Thus 16 individuals, 43%, displayed DI. The lower left lateral incisor (D32) was present in all subjects and thus chosen as an index tooth.

The study hypothesis was tested using linear regression model. We formed two models where the first one had the mesio-distal size of the index tooth as the outcome variable and presence of DI was the explanatory variable. In the second model, the explanatory variable was the type of OI.

RESULTS: Both models yielded the same result: the size of the index tooth did not show significant linear relationship with the presence of DI or the type of OI, p-value threshold being set at 0.05. We obtained similar results using the method of two-way analysis of variance, observing no difference in mean tooth size for different combinations of DI and OI. The results we obtained apply only to the used data and their generalizability is compromised by the small size of the study group and selection of one index tooth.

CONCLUSION: The clinical presence of DI or the type of OI seem not to explain the recently reported OI-associated reduced tooth size (1,2). This finding is clinically important in planning of orthodontic and prosthetic treatment of individuals with OI. The result corroborates the concept that dental manifestations in patients with OI form a continuum from normal dentin structure to severe DI (3) and offers interesting insights into the role of type I collagen in tooth morphogenesis.

FUNDING: Finnish Dental Society Apollonia, Division of Orthodontics; Marjut Evälahti grant to H.T.

P45

Implementation of an Osteogenesis imperfecta patient registry to investigate clinical spectrum and genotype-phenotype correlations in OI

Timothée Ndarugendamwo^{1,2}, Olivia Abegglen^{1,2}, Shajanth Srikantharupan^{1,2}, Pei Jin Lim^{1,2}, Giulio Marcionelli^{1,2}, Christina Kaufman^{1,2}, Cecilia Giunta^{1,2}, Marianne Rohrbach^{1,2}

¹University Children's Hospital, Zürich, Switzerland. ²University of Zürich, Zürich, Switzerland

ABSTRACT

OBJECTIVES: Osteogenesis imperfecta (OI), one of the most common form of skeletal dysplasia, is a genetic heterogeneous disorder characterized by a skeletal dysplasia characterized by reduced bone mass, bone deformities, and fractures. The genetic and clinical heterogeneity of OI is reflected by the identification of 22 causative genes with different modes of inheritance and variable presentation. The historical clinical classification by Silvers describing the severity of the phenotype in 4 types (I-IV) has been expanded to include type V and VI mainly on the basis of skeletal features. However, non-skeletal features such as blue sclerae, hearing loss and dentinogenesis imperfecta are important additional phenotypic component of OI that refine its complex, heterogeneous clinical presentation. This study aims to

describe a single center OI cohort and to investigate genotype-phenotype correlations.

METHODS: Clinical, biochemical, and genetic data of OI patients referred to our center between 1995 and 2022 were retrospectively collected in a REDCap-based register. 168 patients from a gestational age of 22 weeks to the age of 62 years were enrolled, with a female : male ratio of 1.4.

RESULTS: Autosomal dominant inheritance was observed in 55 %, autosomal recessive and X-linked inheritance represented 41% and 4%, respectively. Clinically, OI type I was most frequently diagnosed (29%), whereas severe type III and perinatal lethal type II were diagnosed in 7% and 6% of patients, respectively. Joint hypermobility (44%), fractures (84%), blue sclerae (59 %), short stature (40%), but also dentinogenesis imperfecta (26%) were commonly noted in OI patients. To a lesser degree, respectively 13% and 11%, cardiac abnormalities and hearing loss were observed.

CONCLUSIONS: Beside skeletal hallmarks, non-skeletal features, including blue sclerae, dentinogenesis imperfecta, and even cardiac abnormalities, have emerged frequently among our OI cohort. Additionally, the presence of vertebral fractures which was considered a hallmark of some recessive forms of OI has been found also in patients harboring classical COL1A1/A2 OI variants. This potentializes the investigation of a broader panel of clinical features towards possible genotype-phenotype correlations in Osteogenesis imperfecta.

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The Fate of Bent Telescopic Rods in Children with Osteogenesis Imperfecta: Do All Bent Rods Need to be Revised?

David Fralinger, Denver Kraft, Kenneth Rogers, Richard Kruse, Jeanne Franzone

AI DuPont/ Nemours Children's Health, Wilmington, USA

ABSTRACT

OBJECTIVES: To examine the outcomes on bent telescopic rods that are left in place in children with osteogenesis imperfecta with regards to implant telescoping, fracture healing and re-fracture.

METHODS: Patients with OI at a single institution who underwent lower extremity telescopic rod placement with at least one-year follow-up were identified. Bent rods were identified and for those bone segments we collected location and angle of bend, subsequent telescoping, refracture, increasing angulation of bend and date of revision.

RESULTS: 168 telescopic rods in 43 patients were identified. 46 rods (27.4%) bent during follow-up with average angulation of 7.3° (range 1-24°). 15.7% of rods in patients with severe OI bent compared with 35.7% in non-severe OI ($p=0.003$). The proportion of bent rods was different between independent and non-independent ambulators (34.1%, 20.5%; $p=0.035$). 27 bent rods (59%) were revised, with 12 rods (26%) revised immediately (within 90 days). The angulation of rods that were immediately revised was significantly higher than rods not immediately revised (14.6°, 4.3°, $p<0.001$). Of the 34 bent rods not immediately revised, the average time to revision or final follow-up was 29.1 months. 25 rods (73.5%) continued to telescope, 14 (41%) increased in angulation (average 3.2°) and 10 bones (29%) refractured. Of these refractures, 5 were non-displaced with no increased angulation, 4 showed increased angulation but no loss of fixation, and one was a pilon fracture distal to a tibia rod; none prompted immediate rod revision. Two bones had multiple refractures.

CONCLUSIONS: Bending is a common complication of telescopic rods in the lower extremities of patients with OI. It is more common in independent ambulators and patients with non-severe OI, possibly due to the increased demand placed on the rods. Rods with a small bend and maintained fixation can telescope and need not be an indication for immediate revision. About one third will refracture, but fixation was maintained and the refracture did not require immediate revision in our population. Understanding the fate of bent lower extremity telescopic

rods in the setting of OI can help reduce the overall surgical burden for OI patients during their growing years.

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Altered bone healing mechanoresponse exhibited by mouse models of osteogenesis imperfecta

David Bertrand^{1,2,3}, Kyle Kavaseri^{1,4,3}, Annie-Laurine Sezikeye^{1,3}, Catherine Julien^{1,3}, Reggie Hamdy^{1,3}, Joan C. Marini⁵, Frank Rauch^{1,6}, Bettina M. Willie^{1,2,3}

¹Shriners Hospital for Children, Research Centre, Montreal, QC, Canada.

²Department of Experimental Surgery, McGill University, Montreal, QC, Canada.

³Department of Pediatric Surgery, McGill University, Montreal, QC, Canada.

⁴Department of Biological and Biomedical Engineering, McGill University, Montreal, QC, Canada.

⁵Section on Heritable Disorders of Bone and Extracellular Matrix, NICHD, Bethesda, MD, Canada.

⁶Department of Pediatrics, McGill University, Montreal, QC, Canada

ABSTRACT

OBJECTIVES: Osteotomy followed by intramedullary rodding is commonly used to correct long bone deformities in children with osteogenesis imperfecta (OI). However, it has a high rate of non-union, and individuals with increased mobility are more likely to exhibit delayed healing¹. It is well-known that the mechanical environment surrounding a fracture regulates bone healing, but it is unclear if this process is altered in OI. We aimed to determine the influence of interfragmentary movement on osteotomy healing in two mouse models of OI.

METHODS: To mimic the clinical situation, female Brlt+/-, oim+/-, and their respective WT littermate mice were injected with 0.05mg/kg zoledronic acid from 5 to 9 weeks of age. At week 10, a 0.5mm femoral osteotomy was performed, stabilized with a rigid or semi-rigid external fixator, allowing different magnitudes of interfragmentary movement. Bone healing was assessed by *in vivo* microCT (n=10 mice/genotype) at 0, 7, 14, 21, and 28 days, as well as ongoing histomorphometry and torsional testing (additional cohort, n=10 mice/genotype) at day 28. We assessed the effects of genotype, fixation stiffness, scan day and interactions by ANOVA with Tukey's post-hoc tests.

RESULTS: Mineralized tissue volume (BV) was increased in oim and Brlt WT littermates with osteotomies stabilized with semi-rigid versus rigid fixation ($p<0.05$). However, no difference in BV was observed between fixation stiffnesses in oim+/- or Brlt+/- mice. Total callus volume (TV) was increased with semi-rigid fixation compared to rigid fixation for all genotypes ($p<0.02$), with the exception of the Brlt+/- mice ($p=0.09$).

At day 28, healing was similar between oim+/- or Brlt+/- and their respective WT under both rigid and semi-rigid fixation. There were no differences between Brlt+/- and oim+/- mice, but BV/TV and BMD were significantly increased in oim WT compared to Brlt WT mice ($p<0.02$).

CONCLUSION: Fixation stiffness modulated the healing response in terms of mineralized tissue formation in WT, but not OI mice, indicating an altered mechanoresponse. Healing differences observed between WT littermates of oim and Brlt mice may be due to differing genetic backgrounds².

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Ophthalmological screening guidelines for individuals with osteogenesis imperfecta : a scoping review

Sarah Moussa¹, Reggie Hamdy², Argerie Tsimicalis², Jakob Grauslund³, Marie Louise Lyster³

¹McGill University, Montreal, Canada. ²Shriners Hospital, McGill University, Montreal, Canada. ³Odense University Hospital, Department of Ophthalmology, Odense C, Denmark

ABSTRACT

OBJECTIVE: Osteogenesis imperfecta (OI) is a collagen disorder in which Type 1 collagen is defective. The eye is a structure rich in collagen Type 1 and is therefore heavily impacted by the disease. Many vision threatening eye diseases have been associated with OI. They also occur at an earlier age in individuals with OI. Despite the research done on these risks, little is known about the appropriate ophthalmological screening for individuals with OI. As such, the purpose of this review is to describe the available ophthalmological screening as described in the literature to help inform the creation of guidelines.

METHOD: A scoping review based on the Joanna Briggs Institute (JBI) methodology was conducted². In consultation with a research librarian, a search of databases (Medline, Web of Science, Embase) was completed. Primary sources who matched the inclusion and exclusion criteria were then screened, extracted, and analyzed using Covidence.

RESULT: A total of 32 primary articles met inclusion and exclusion criteria, containing case reports, case series and cohort studies. Despite the high risk of blindness associated with the consequences of OI on the eye, the primary literature fails to provide detailed screening guidelines aimed at identifying disease early.

CONCLUSION: It is important to further investigate ophthalmological screening opportunities for individuals with OI, thus limiting these vision threatening risks with early detection and treatment. Standardized ophthalmological screening guidelines for OI remain an area for research.

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P49

Oral health related quality of life in adults with osteogenesis imperfecta, in Spain

Amira Ahmed Ali Elfituri, Joaquín De Nova
Complutense University of Madrid, Madrid, Spain

ABSTRACT

OBJECTIVE: The objective of this study is to explore the influence of severity of OI on quality of life related to oral health in adults resident in Spain. **METHOD:** Adults with OI, recruited from AHUCE Foundation that serves individuals with a clinical and/or molecular diagnosis with OI in Spain. OHRQoL is evaluated using the resuned Oral Health Impact Profile questionnaire (OHIP-14sp). **RESULTS:** A total of 52 participant (67% women) classified as mild, moderate and sever clinical symptoms groups of OI (n= 13,26 and 13, respectively). OHIP-14sp scores were significantly higher (i.e., worse) for OI sever group [SD 27] than for mild and moderate groups [SD 16, 17.5] (P < 0.05). The difference between OI types found in psychological disability, social disability and handicap domains, as OI sever group is associated with significantly higher grade compared to OI mild group. **CONCLUSION:** The severity of OI impacts OHRQoL in adults.

KEYWORDS: Osteogenesis imperfecta, oral health-related quality of life, Oral Health Impact Profile

P50

Lack of psychosocial intervention assessment in OI: a narrative literature review

Marie-Catherine Mongenot, Yu Chen Shi, Reggie Hamdy, Argerie Tsimicalis

McGill, Montreal, Canada

ABSTRACT

OBJECTIVES: Osteogenesis imperfecta (OI) is a heritable bone fragility disorder leading to physical limitations and frequent fractures. Feeling different, fearing fractures, and dealing with physical and social barriers are some of the psychosocial challenges of individuals living with OI. The goal of the present narrative literature review was to assess what psychosocial interventions have been studied so far, or are included in OI management, with the goal of formulating suggestions on the psychosocial component of patient care management.

METHODS: Following the Ferrari best practice recommendations for the preparations of a narrative review in the clinical field, Medline, EMBASE, CINAHL, Cochrane library and PsychInfo databases were searched, following a search strategy designed in consultation with a research librarian. Primary sources respecting the inclusion and exclusion criteria were selected and articles were critically assessed and the results reported.

RESULTS: 19 articles were included. Despite many articles highlighting the psychosocial impact of OI, and the need for including this aspect in the management of patients, no study has yet assessed which interventions are best suited to this specific population. Only one article on OI management, from the UK, included a description of different possible psychosocial interventions available to OI patients. Furthermore, depending on the type of OI, psychosocial experience of patients can greatly differ. As a matter of fact, milder OI presentations (type I) face different challenges due to their normal appearance covering their underlying fragility. Studies on psychosocial experience of OI population tend to be biased by more frequently studying individual of the severe type, Type III, or by not precising and stratifying the different OI presentations included in the study.

CONCLUSION: The necessity of offering psychosocial interventions to OI individuals to support them in the physical, environmental, and emotional challenges they are faced with is well established in literature. However, there is a need to assess which interventions are best suited to help this specific population, and to come up with guidelines including the psychosocial aspect of the disease in care management. Also, the different OI types should be considered separately as they are not necessarily faced with the same daily challenges.

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***Ifitm5*/BRIL p.S42L murine model for atypical type VI OI has elevated serum alkaline phosphatase and disordered bone matrix but decreased bone cell function**

Gali Guterman-Ram^{1,2}, Ghazal Hedjazi^{3,4}, Milena Jovanovic¹, Chris Stephan⁵, Aileen Barnes¹, Stéphane Blouin³, Victoria Schemenz⁶, Markus A. Hartmann³, Theresa Hefferan⁷, Pamela Robey⁸, Peter Fratzl⁶, Jochen Zwerina³, Kenneth M Kozloff⁵, Nadja Fratzl-Zelman³, Joan C Marini¹

¹Section on Heritable Disorders of Bone and Extracellular Matrix, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, USA. ²Faculty of Biomedical Engineering, Technion—Israel Institute of Technology, Haifa, Israel. ³Ludwig Boltzmann Institute of Osteology at Hanusch Hospital of OEGK and AUA Trauma Centre Meidling, 1st Med. Dept. Hanusch Hospital, Vienna, Austria. ⁴Lifebrain, 1140, Vienna, Austria. ⁵Departments of Orthopaedic Surgery and Biomedical Engineering, University of Michigan, Ann Arbor, USA. ⁶Max Planck Institute of Colloids and Interfaces, Dept. of Biomaterials, Potsdam, Germany. ⁷Mayo Clinic, Biomaterials and Histomorphometry Core Laboratory, Rochester, USA. ⁸Craniofacial and Skeletal Diseases Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, USA

ABSTRACT

Type V osteogenesis imperfecta (OI), caused by recurrent dominant mutation in *IFITM5*/BRIL, and type-VI OI, caused by recessive null mutations in *SERPINF1*/PEDF, have distinct phenotype, inheritance, bone histology and osteoblast differentiation. The *IFITM5*-p.S40L leads to atypical type-VI OI (aVI), reported in 10 patients, with severe dominant OI with phenotype, bone histology and decreased cellular secretion of PEDF similar to type-VI OI, rather than Type-V OI.

We generated an *Ifitm5*/BRIL p.S42L knock-in mouse to understand the connection between *IFITM5* and *SERPINF1* in bone development. Male mice were analyzed using X-Ray, serum chemistry, aBMD, qBEI, SHG, μ CT, bone mechanics, histology and in-vitro OB differentiation.

Newborn *Ifitm5*/BRIL p.S42L mice, both heterozygous(HET) and homozygous(HMZ), are non-lethal, have flared rib cage, shoulder, and knee dislocations. Spontaneous fractures occur in heterozygotes and homozygotes. Similar to aVI OI patients, young heterozygous mice have normal serum PEDF level and increased serum ALP(p<0.01). Both HET and HMZ have decreased bone strength and markedly increased brittleness. HET mice have decreased Ct.Th but increased metaphyseal BV/TV, Tb.N and 3rd trochanter vascular pore volume/BV. Whole-body DXA-aBMD was significantly decreased(p<0.01). qBEI revealed hypermineralization in 1- and 2-month-old heterozygous mice, with increased CaMean, CaPeak(p<0.05) and tripling of CaHigh in cortical bone(p<0.01). Increased mineral was deposited by cultured calvarial osteoblasts from heterozygous mice(p<0.05). Heterozygous mice femora contain mostly disordered matrix (p<0.0001) by SHG. Under polarized light, heterozygous bone has mixed lamellar and disordered areas, while homozygous bone is disorganized. Surprisingly, osteoid(OS/BS) was decreased on histomorphometry in 1-month-old mutant mice, as were bone cellularity (osteoblasts and osteoclasts), MAR and BFR/BS. Osteocyte lacunar density was increased but area decreased(both p<0.001) by qBEI. PEDF secretion from differentiating osteoblasts of heterozygous mice was decreased only on Day 1. Collagen secretion by HET calvarial osteoblasts was significantly increased (p<0.05).

Our murine model with physiological expression of *Ifitm5*/BRIL p.S42L recapitulates bone hypermineralization plus increased CaHigh, and patchy matrix disorganization of type VI OI patients, although other aspects of *Ifitm5*/BRIL p.S42L bone cell function resemble type V OI. Multiple findings point to a connection of late osteoblast/osteocyte function and abnormal matrix organization and mineralization.

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P52

Experience, problems and prospects of development of the program of diagnostics and treatment of osteogenesis imperfecta in children in the Republic of Kazakhstan

Dossanov Bolat¹, Lozovoy Vasiliy¹, Khmyzov Sergei², Dossanova Assem¹, Baidullaev Erkinbek¹, Nukina Zhanerke¹

¹JSC Medical University Astana, NurSultan, Kazakhstan. ²Institute of Pathology of the Spine and Joints. prof. M.I. Sitenko, Kharkov, Ukraine

ABSTRACT

AIM: Discussion of the process implementation of the program for the diagnosis and treatment of the osteogenesis imperfecta in children in the Republic of Kazakhstan (RK).

MATERIALS: In Kazakhstan, the problem of osteogenesis imperfecta (OI) in children became interested in the framework of scientific research for the first time in 2015 at the Department of Pediatric Surgery of JSC "Astana Medical University (AMU)".

At the initiative of the parents, in 2018, a group of scientists from the AMU registered an Initiative Research Work on the topic: "Applied Research of Hereditary and Systemic Diseases of Cartilage and Bone Tissue in Children" No. 0118RKI0601 dated 11/15/2018, for 5 years.

However, in the work of the project, there were difficulties. One of the initial problems was that drugs of the bisphosphonate group were recommended for use from the age of 18, which was contrary to the protocols in the RK. Therefore, by order of the meeting of the ethical commission of the Ministry of Health, it was decided to carry out treatment after receiving the voluntary consent of the parents, and the Competence Center for the treatment of patients was determined. The next questions were the choice of the type and registration of telescopic implants. In 2021, the Center for Diagnosis and Treatment of Rare Bone Pathology was opened in the capital, on the basis of which, together with NAO MUA, 6 operations were successfully performed for the first time to install intramedullary telescopic Fassier-Duval "Pega Medical" telescopic implants.

RESULTS: Changes were made to the protocol for the diagnosis and treatment of OI in children (Protocol №11 dated Sept. 29, 2016), a Qualification Center was based on the JSC "National Scientific Institute of Motherhood and Childhood", and a centre for the Public Association "Patients with rare areas of bones" was created.

The existing metal structures have several limitations and are unacceptable for the healthcare of the Republic of Kazakhstan, therefore we are introducing and implementing domestic metal structures.

CONCLUSIONS: Despite the fact that in the Republic of Kazakhstan there are significant achievements in providing medical care to children with OI, there are still gaps in genetic diagnosis, rehabilitation and psychosocial support.

P53

Clinical management of the adult patient with Osteogenesis Imperfecta

Arjan GJ Harsevoort^{1,2}, A.F.M. van der Grijn¹, K Gooijer³, A.M.V. Domisse¹, H.M. Bout³, M.W. Elting², m De Jong¹, J Feenstra¹, G.J.M. Janus¹

¹Isala Hospital, Zwolle, Netherlands. ²UMC, Amsterdam, Netherlands. ³Isala Hospital, Zwolle, Netherlands

ABSTRACT

OBJECTIVE: Osteogenesis Imperfecta [OI] is a rare genetic disorder with a wide variation in clinical characteristics. Therefore, it is preferable that OI is treated by a multidisciplinary team (MDT). In other rare disorders, a multidisciplinary approach has shown promising results, which suggests that a multidisciplinary approach may also be beneficial for patients with OI. In this abstract we describe the development of standardized multidisciplinary approach in patient with OI in the ISALA

OI Expert Center, which may serve as a blueprint for the management of OI patients in health care systems throughout the world.

METHODS: The development of a multidisciplinary OI outpatient clinic is described in four steps, derived from the start and development of a Multidisciplinary Team for the treatment of patients with OI in the Netherlands.

RESULTS: The first step is to set up collaboration and coordination together with patients, by working with the patients' association of OI in the designated country. This first step is essential to gain insight into the patients' needs. A coordinator needs to be assigned to the team to monitor progress.

The second step is to establish a core team which includes the coordinator, an orthopedic surgeon, an endocrinologist, an occupational therapist, and a rehabilitation physician. This core team ensures the basic care for all patients.

The third step is to expand the MDT with specialized care for individual cases by adding specialists for example a neurologist, a cardiologist or a clinical psychologist

The last step is to professionalize the care for OI-patients by means of shared-decision making. This step can be facilitated by the manual for standardized care as proposed by Key4OI International, which focuses on shared decision-making. This leads to more effective and meaningful treatment and will contribute to (scientific) knowledge about OI.

CONCLUSION: To ensure the quality of care for patients with OI, a multidisciplinary approach is necessary. Setting up a MDT requires dedication and time from motivated specialists working in close cooperation with other specialists, individual patients and their relatives and representatives. Shared-decision making will increasingly be used to satisfy the needs of individual patients. This approach yields promising results

P54

Patient Reported Experience Of Clinical Care Of Osteogenesis Imperfecta (OI) During The COVID-19 Pandemic

Debra Smyth¹, Monica Hytiris¹, **Coreen Kelday**², Ciara McDonnell³, Christine Burren⁴, Adrian Gardner⁵, Lisa Mills⁶, Susan Parekh⁷, Joerg Semler⁸, Angie Stewart⁹, Ingunn Westerheim¹⁰, Kassim Javaid¹¹, Patricia Osborne⁹, SF Ahmed¹

¹Office for Rare Conditions, University of Glasgow, Glasgow, United Kingdom.

²Brittle Bone Society, Dundee, United Kingdom. ³Department of Paediatric Endocrinology & Diabetes, Children's Health Ireland, Dublin, Ireland.

⁴Department of Paediatric Endocrinology and Diabetes, Bristol Royal Hospital for Children, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, United Kingdom. ⁵Royal Orthopaedic Hospital, NHS Foundation Trust, Birmingham, United Kingdom. ⁶Bristol Royal Hospital for Children, University Hospitals Bristol and Weston NHS Foundation Trust, Birmingham, United Kingdom. ⁷Department of Paediatric Dentistry, UCL Eastman Dental Institute, University College London, London, United Kingdom. ⁸University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Paediatrics, Cologne, Germany. ⁹Brittle Bone Society, Glasgow, United Kingdom. ¹⁰Osteogenesis Imperfecta Federation Europe, OIFE, Netherlands.

¹¹Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Nuffield Orthopaedic Centre, University of Oxford, Oxford, United Kingdom

ABSTRACT

OBJECTIVES: Research on the effects of the COVID-19 pandemic on people with rare diseases is limited. Few studies compare healthcare throughout the progression of the ongoing pandemic. The aim of this study was to assess the impact of lockdown on individuals with OI (Osteogenesis Imperfecta) across two consecutive pandemic years, to understand what challenges were encountered, and to analyse the experience of remote consultation.

METHODS: Two independent surveys were distributed in August 2020 and April 2021. The primary survey was distributed following the first lockdown, and the second survey built on the experiences reported from the initial survey. The surveys explored four key themes- effects on

therapy, alternatives to consultation, effect on mental health, and perceived risks of COVID-19.

RESULTS: In the primary 2020 survey of the 110 respondents 69 (63%) had at least one appointment delayed due to lockdown, increasing to 89 of the 124 respondents (72%) in the follow-up survey. Of the 110 initial survey participants, 57 (52%) had a remote consultation, increasing to 92 of 124 (74%) in the follow-up survey. In the primary survey 63 of 91 (69%) expressed increasing anxiety due to lockdown, compared with 76 of 124 (61%) in the follow-up survey. In the primary survey 12 of 91 respondents (13%) expressed concerns at not seeing friends and family compared with 103 of 124 (83%) in the follow-up survey. In the second survey of 124 participants there were concerns regarding weight and diet (55, 44%), mobility (70, 56%), pain (71, 57%), and keeping physically active (89, 72%). The majority of participants felt they would have a worse illness and require longer rehabilitation than someone without OI (81 of 117 respondents, and 77 of 120 respectively), and the majority of participants (68%) had been vaccinated at the time of the second survey.

CONCLUSION: The pandemic has had widespread effects on both the mental and physical health of those with OI. These repercussions are likely to be felt for years to come. On the other hand, the pandemic has also revealed that in certain situations remote consultation may prove a viable long-lasting alternative to face-to-face appointments.

P55

A Dual centre transition clinic for young people with mild, moderate and severe Osteogenesis Imperfecta

Mark Heathfield¹, **Martyn Dudley**², Judith Bubbear², Richard Keen², Sophie Barlow², Friederike Baldewag², Catherine DeVile¹

¹Great Ormond Street Hospital for Children, London, United Kingdom. ²Royal National Orthopaedic Hospital NHS Trust, London, United Kingdom

ABSTRACT

OBJECTIVES: We aim to demonstrate the experiences of young people aged between 17 and 25 years of age who attended the Osteogenesis Imperfecta (OI) transition clinic, with mild, moderate, or severe OI within the last 2 years, and improvements they would recommend. This service is run jointly by the Royal National Orthopaedic Hospital (RNOH) Metabolic bone service, and Great Ormond Street Hospital for Children (GOSH) Highly Specialised OI Service.

METHODS: A questionnaire was sent out to all patients seen in the OI transition clinic in the last 2 years, responses were anonymised. Phone calls were made to patients who did not have email addresses listed on their NHS record. To increase the response rate, this was conducted by the Clinical Nurse Specialists from both hospitals with administrative support. The survey will be conducted for 12 months after each appointment to monitor the changes made as a result of this work. This project is registered with RNOH and GOSH audit teams.

RESULTS: The full results are forthcoming to ensure a sample size large enough to make effective changes to the operation of future clinics, ensuring patient views are considered as part of changes made.

CONCLUSION: Transition is an important process for young people moving from paediatric to adult healthcare services. It is hoped that anxieties surrounding this process can be reduced through effective collaboration between paediatric and adult services. The thoughts and experiences of patients who have recently completed this process are valuable to ensure that the clinic provides both expert medical care, whilst meeting needs and expectations of the patients.

P56

Genetics of Rare Skeletal Disorders among Pakistani Consanguineous Families

Mehran Kausar¹, Saima Siddiqi², Mariam Anees³

¹Karakorum International University, Gilgit, Pakistan. ²Institute of Biomedical and Genetic Engineering, Islamabad, Pakistan. ³Quaid-i-Azam University, Islamabad, Pakistan

ABSTRACT

OBJECTIVES:

- Identification and sampling of Pakistani consanguineous families with skeletal dysplasias.
- Clinical characterization of disease followed by extraction of DNA from blood samples and identification of the genetic cause in multiple consanguineous families by applying various molecular/sequencing platforms.

MATERIALS AND METHODS: We present, thirteen (Family 1 - Family 13) unrelated Pakistani consanguineous families with skeletal dysplasias those were identified and recruited for genetic/molecular characterization. After drawing the pedigrees of the affected families, comprehensive clinical examination of affected individuals was done followed by deploying of diverse molecular techniques on DNA samples of affected families including polymerase chain reaction, direct sequencing of relevant genes, microarray, exome-sequencing and Sanger sequencing to investigate the exact underlying genetic causes in patients.

RESULTS: We were able to identify eleven novel biallelic sequence variants including three missense mutations, five frameshifts, one nonsense mutation, one small deletion and one large deletion in various genes among the affected families. Apart from novel variants, we also identified two already known biallelic sequence variants in two genes. Novel pathogenic missense variants included p.Gly324Cys in WNT1 in Family 1, p.Leu197Pro in CHST3 in Family 7 and p.Leu165Pro in ECEL1 in Family 9. Novel highly deleterious homozygous frameshifts included were p.Arg840Thrfs_115 in XYLT2 in Family 2, p.Leu275fs*22 in FKBP10 in Family 3, p.Thr196fsTer in SERPINF1 in Family 4, p.Met180fsTer in PAH in Family 11 and p.Asp259fsTer in MKKS in Family 12. A novel nonsense mutation p.Tyr201* in CHST3 was recognized in Family 8. A small deletion of one amino acid (p.Phe275del) in SERPINF1 was found in Family 5 and a large multi exonic deletion p.Asp3306Lysfs*7 in ALSM1 was identified in Family 10. Two recurrent variants included p.Arg166His in SPARC in Family 6 and p.Arg46Trp in CTSK in Family 13. All these mutations were found to be highly deleterious.

CONCLUSION: The present study unveils that skeletal dysplasias are highly heterogeneous genetic disorders and perhaps there could be involvement of many more genes in their pathogenicity. Identification of novel genes indicates the involvement of specific molecular pathways and consequently helps in devising genotype-phenotype correlation. Establishment of a gene pool of affected genes would provide basis for gene editing using state-of-the-art gene tools in future.

P57

Prevalence and Hospital Admissions in Patients With Osteogenesis Imperfecta in The Netherlands: A Nationwide Registry Study

Silvia Storoni^{1,2,3}, Sanne Treurniet^{1,2,3}, Alessandra Maugeri^{4,2,3}, Gerard Pals⁴, Joost G. van den Aardweg⁵, Stéphanie L. van der Pas⁶, Mariet W. Elting⁴, Peter Kloen^{7,2,3}, Dimitra Michal^{4,3,2}, Elisabeth Marelise W. Eekhoff^{1,3}

¹Amsterdam UMC Location Vrije Universiteit Amsterdam, Department of Internal Medicine Section Endocrinology, Amsterdam, Netherlands. ²Amsterdam Movement Sciences, Tissue Function and Regeneration, Amsterdam, Netherlands. ³Amsterdam UMC, Amsterdam Bone Center, Amsterdam, Netherlands. ⁴Amsterdam UMC Location Vrije Universiteit Amsterdam, Department of Human Genetics, Amsterdam, Netherlands. ⁵Amsterdam UMC Location Vrije Universiteit Amsterdam, Department of Respiratory Medicine, Amsterdam, Netherlands. ⁶Amsterdam UMC Location Vrije Universiteit Amsterdam, Department of Epidemiology and Data Science (EDS), Amsterdam, Netherlands. ⁷Amsterdam UMC Location Vrije Universiteit Amsterdam, Department of Orthopedic Surgery, Amsterdam, Netherlands

ABSTRACT

OBJECTIVES: Osteogenesis Imperfecta (OI) is a complex disease caused by genetic alterations in production of collagen type I, and collagen-related proteins. Bone fragility is the most common patient issue, but extraskelatal complications also present an adverse factor in the quality of life and prognosis of patients with OI. However, still little is known about the morbidity and mortality of these patients. The objective of this paper is to determine and describe to what extent OI impacts patients' life in terms of hospitalization and complications describing the incidence and prevalence of the Dutch cohort of OI patients and the characteristics of their hospital admissions.

METHODS: Information regarding OI patients and their hospital admission was extracted from the Statistics Netherlands Database and matched to the OI Genetics Database of Amsterdam UMC.

RESULTS: Hospital admission data was available for 674 OI patients. This OI nationwide registry study shows that the life expectancy of OI patients is adversely affected by the disease. The median annual incidence risk of OI between 1992 and 2019 was 6.5 per 100,000 live births. Furthermore, patients with OI had a 2.9 times higher hospitalization rate compared to the general Dutch population. The highest hospitalization rate ratio of 8.4 was reported in the patient group between 0 and 19 years old.

CONCLUSION: OI type and severity had impact on extraskelatal manifestations, which play a key role in the numerous hospital admissions. More awareness about the impact of OI on patients' life is needed to improve and implement prevention and follow-up guidelines.

P58

The European Registry for Rare Bone and Mineral Conditions (EuRR-Bone): Results of a Survey on Osteogenesis Imperfecta

Ana Luisa Priego Zurita¹, Oana O Danila¹, Maria Luisa Brandi², Jillian Bryce³, Iveta Dzivite-Krisane⁴, Wolfgang Högl⁵, Rodrigo Montero-Lopez⁵, Geert Mortier⁶, Ralf Oheim⁷, Jose A Riancho⁸, Luisa de Sanctis⁹, S Faisal Ahmed^{1,3,10}, Natasha M Appelman-Dijkstra¹

¹Department of Medicine, Division of Endocrinology, Leiden University Medical Centre, Leiden, Netherlands. ²Fondazione Italiana Ricerca Sulle Malattie dell'osso (F.I.R.M.O. Foundation), Florence, Italy. ³University of Glasgow, Office for Rare Conditions, Glasgow, United Kingdom. ⁴Children's Clinical University Hospital, Riga, Latvia. ⁵Department of Paediatrics and Adolescent Medicine, Johannes Kepler University Linz, Linz, Austria. ⁶Centre of Human Genetics, UZ Leuven, Leuven, Belgium. ⁷University Medical Center Hamburg-Eppendorf, Hamburg, Germany. ⁸Department of Internal Medicine, Hospital U M Valdecilla, University of Cantabria, Idival, Santander, Spain. ⁹Pediatric Endocrinology, Regina Margherita Children Hospital-AOU Città della Salute e della Scienza, Torino, Italy. ¹⁰University of Glasgow, Developmental Endocrinology Research Group, Royal Hospital for Children, Glasgow, United Kingdom

ABSTRACT

INTRODUCTION: EuRR-Bone offers an electronic reporting system (e-REC) that captures the occurrence of rare conditions within reference networks such as ERN BOND and Endo-ERN. Secondary surveys following the reported cases in e-REC collect a brief amount of data for understanding the clinical presentation of the reported condition. Osteogenesis Imperfecta (OI) is a rare condition that requires expert care but the extent of variation in care delivery across expert centres is unclear.

METHODS: Between May 2020 and May 2021, 76 OI cases were reported in e-REC. Reporters were invited to complete a secure online questionnaire. The questionnaire was completed in 35/76 cases (46%) by 6 centres from 5 countries.

RESULTS: The median age at presentation was 3 years (range 0, 47). Medical history, clinical findings and imaging were part of the diagnostic workup in all cases of OI. Of 31 confirmed cases, 30 had genetic testing (97%). Regarding the clinical type of OI, 18 (58%) had type I, 6 (19%) had type IV, 2 (6%) had type III and in 4 cases the type was not specified. Mobility was assessed in 16/31 (51%) OI cases, using clinical data in 43%, and a 6-minute walk test in 25%. Deformities were reported in 21 (67%) patients with those in the lower limbs being the most frequently reported (51%) followed by spine deformities (32%) and upper limb deformities (19%). Cardiovascular morbidity was investigated in 16/31 (52%) and pulmonary problems were reported in 1/31 (3%). Quality of life was assessed in 32% of OI cases (10/30 paediatric patients) using anamnesis and clinical data in all cases: the use of validated questionnaires, such as EQ-5D, was not reported.

CONCLUSION: Although the clinical care of OI at expert centres is variable, there are some outcomes that are collected routinely by the majority of them. This survey supports the development of unified standard of care in the form of a core dataset across centres, and provides the basis for the development of a disease-specific module within the registry.

P59

How we made an Impact – The role of Patient Advocacy Groups in recruitment to surveys on rare conditions

Ingunn Westerheim¹, Frank Rauch², Taco van Welzenis¹, Oliver Semler³, Tracy Hart⁴, Katherine Bache⁴, Michael B. Bober⁵, Cathleen Raggio⁶, Lena Lande Wekre⁷, Ruari O'Donnell⁸, Samantha Prince⁸, Maria Rapoport⁸

¹Osteogenesis Imperfecta Federation Europe (OIFE), Heffen, Belgium. ²McGill University, Montreal, Canada. ³University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Paediatrics, Cologne, Germany. ⁴Osteogenesis Imperfecta Foundation (OIF), Gaithersburg, Maryland, USA. ⁵Alfred I. duPont Hospital, Wilmington, Delaware, USA. ⁶Hospital for Special Surgery, New York, USA. ⁷TRS National Resource Center for Rare Disorders, Sunnaas Rehabilitation Hospital, Nesodden, Norway. ⁸Wickenstones, Abingdon, United Kingdom

ABSTRACT

OBJECTIVES: Internet-based surveys are important tools for collecting information on rare conditions. However, recruitment of participants can be difficult, as individuals with rare conditions are exposed to large numbers of questionnaires, leading to 'survey fatigue'.

Here we highlight strategies used by two patient advocacy organizations (PAO), the Osteogenesis Imperfecta Federation Europe (OIFE) and the Osteogenesis Imperfecta Foundation (OIF), to increase participation in the recent IMPACT survey on OI.

METHODS: The 80-item survey was a joint initiative between OIFE, OIF and Mereo BioPharma. It was aimed at learning about patient journey, quality of life and economic impact, targeting individuals with OI above 12 years of age and caregivers. The project was initiated by the industry partner, but PAOs will determine data use. The PAOs had a large influence on survey questions and translations and sought input from members. The project was initiated in April 2020 and was first presented to the OI-organizations in June 2020. Regular updates were provided before launch.

RESULTS: The survey was open from July 1 to September 30, 2021, and was available in eight languages. Recruitment numbers were analyzed and communicated in weekly updates. Online talks about the survey in membership meetings in local language, created awareness in the community.

Communication materials (such as key messages hashtags, banners, frames) were mostly developed by the PAOs. An element of friendly competition was introduced by providing weekly country-specific recruitment numbers, highlighting countries with high recruitment rates. Inclusion of 'submit' buttons on each survey section allowed saving partial data. About 2200 participants from 65 countries provided full responses. Data analysis is ongoing.

CONCLUSIONS: This is the largest survey on OI that has been conducted until now. A key aspect for successful recruitment was ownership of the project and data by PAOs, creating trust in the community. Target population was informed about the project early (more than 1 year before launch) and repeatedly. An element of competition helped sustain recruitment rates while the survey was open.

By taking on a key role in the project, PAOs could show to potential participants the purpose of the survey and "what's in it for them".

P60

Sleeping Compression - Lengthening Nail; Off-label use for treatment of non union then lengthening in Osteogenesis Imperfecta patient

Yasser Elbatrawy, Ahmed Hammouda
Al-Azhar University, Cairo, Egypt

ABSTRACT

Is it effective to activate a PRECICE internal lengthening nail with remote control for lengthening after using it for shortening to treat non

union in Osteogenesis Imperfecta patient then compensate the resulted limb discrepancy few years later?

This is a case report for a boy 15 years old, diagnosed with Osteogenesis Imperfecta underwent several previous surgeries for both femoral and tibial bones with history of poor and delayed union. Three years ago, he had non-united sub-trochanteric left femur fracture fixed with regular IMN with limb length discrepancy of 2 cm. He underwent first surgery with debridement & bone grafting and exchange of the nail with suitable size lengthening PRECICE nail. We used the fast intra operative remote control to distract the nail, so we can use it to compress the non union site aiming for union. A second surgery was performed 2.5 years later to activate the sleeping PRECICE nail after making mid-shaft osteotomy through minimal incision to equalize the limb length. Osteotomy location was decided in consideration for the safety location guided by the PRECICE users.

RESULTS: After the first surgery in February, 2019; the subtrochanteric non union healed completely within 5 months. At the second surgery in August 2021, the remote control was adjusted to lengthen the femur at a rate of 0.6 mm./ day divided on 3 times and completed 2 cm of length. Gradual observation of regenerate healing was observed till completing union at 9 months follow up after the second surgery. No complications were noticed and the patient is able to full weight bearing. Femur length is equalized with preserved knee and hip range of motion.

CONCLUSION: Instead of re-inserting another lengthening nail which is a major surgery, it is useful to re-use the existing PRECICE nail to activate or resume lengthening after doing adequate osteotomy. This would be helpful and provide an alternative economic safe option for selected cases; however, it is considered to be off-label use.

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Skull fractures, cervical spine fractures and intracranial injuries in children with Osteogenesis Imperfecta: a cohort study

Georgina Williams¹, Jeremy Allgrove², Alistair Calder^{2,3}, Belinda Crowe², Mark Heathfield², Catherine DeVile²

¹Division of Medicine, University College London, London, United Kingdom.

²Osteogenesis Imperfecta Service, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom. ³Department of Radiology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom

ABSTRACT

BACKGROUND: Research into childhood Osteogenesis Imperfecta (OI) has typically focused on long-bone and vertebral fractures. Such injuries are commonly found at clinical presentation associated with minimal trauma. There is paucity of literature on other fractures, particularly those of the skull and cervical (C)-spine, and intracranial injuries, despite potentially serious consequences.

OBJECTIVES:

- Establish the prevalence of skull fractures, C-spine fractures and intracranial injuries without associated skull fractures in patients with OI.
- Explore related mechanisms of injury, clinical outcomes, and detection protocols.

METHODS: A quantitative, retrospective cohort study of children aged 0–19 years, under the OI service at Great Ormond Street Hospital, who were identified as having a skull fracture, C-spine fracture, or intracranial injury without associated fracture. Data were collected from the current Electronic Patient Record system and historical paper-based records. Descriptive and statistical analyses were performed.

RESULTS: 27 confirmed injuries were identified from 331 patient records: 17 skull fractures, 7 C-spine fractures, and 3 intracranial injuries without associated fracture. Most injuries occurred in infancy with only 2 occurring in adolescence. The majority had a traumatic cause (n=17, 63.0%), namely falls. However, 3 fractures were found on routine screening. Skull fractures mostly affected the parietal bone and all C-spine fractures affected C1 and/or C2. Most children with C-spine fractures had severe OI. The majority (n=21, 77.8%) required CT

diagnostic imaging. Twenty-five (92.6%) patients had no neurological sequelae. A significant difference was found between the proportion of patients with severe OI in the sample and cohort populations, at $p < 0.05$. There was no correlation between injury mechanism and clinical outcome.

CONCLUSIONS: Results indicate low prevalence of these injuries: 8.16%. Notably three fractures were found incidentally, highlighting the need for radiological screening. Results suggest a necessary low threshold for imaging children with OI who present with potential head or neck injuries. This is paramount in severe OI, where significant injury can occur with minimal trauma. We advocate study expansion to other hospitals both in the UK and internationally. Further study is required to add to current knowledge, and identify optimum diagnostic and imaging approaches; ensuring best-possible outcomes for head and neck injuries in children with OI.

P62

Long-Term Results of Initial and Reoperation Surgeries with Fassier-Duval Intramedullary Rods in Femurs and Tibias of Children with Osteogenesis Imperfecta

Adriano DellaPolla¹, Kaeli Samson², Arianna Dalamaggas¹, Elizabeth Strudthoff², Paul Esposito², Maegen Wallace²

¹Creighton University, Omaha, USA. ²University of Nebraska Medical Center, Omaha, USA

ABSTRACT

OBJECTIVES: Osteogenesis imperfecta (OI) is a genetic connective tissue disorder affecting type I collagen, which is integral for the strength of osseous tissue. OI has a heterogeneous molecular inheritance pattern – divided into four major subgroups (I–IV). Children with OI suffer from multiple fractures and bony deformities often requiring surgical intervention with osteotomies and intramedullary telescoping rods. Our study examined the relationship between initial and reoperation indications for femur and tibia Fassier Duval (FD) rodding surgeries in OI patients based on age, bone and OI type.

METHODS: Retrospective chart review of initial FD rod surgeries included 197 bones (femurs and tibias) from 58 patients. Reoperations included 140 bones from 45 patients. Variables included age at first operation (0–24, 24.1–48, 48.1+ months), time to reoperation, operation indications, bone, and OI type. Spearman correlations were used separately for each bone type to assess associations between age at first surgery and total number of surgeries. To assess dichotomous outcomes, generalized estimating equations were utilized and adjusted for bone type and side. Kaplan-Meier curves were generated to display time to reoperation, stratified by OI type and bone-type. Data was collected from 2003–2018. IRB approval was obtained. Analyses were performed using SAS software v9.4

RESULTS: There was a statistically significant association between age at first surgery and indication (bowing and fracture) for initial surgeries ($p < 0.0001$ and $p = 0.01$, respectively) but these associations were not significant for reoperation surgeries. All bones, except left tibias, had significant negative correlations between age at first surgery and total number of surgeries. Tibias had 2.39 times the risk of reoperation than femurs within type III patients, but there was no significant difference in bone types within type IV patients. In addition, older patients had a significantly lower risk of reoperation.

CONCLUSION: Bowing and fractures are the most common causes for initial surgeries in children with OI. Patients in older age groups at first surgery need fewer reoperation surgeries. The risk of reoperation is higher for tibias than femurs in Type III patients and is generally lower in older patients.

Survivability of FD rods is associated with age of first surgery and bone.

P63

Impact of pandemic on self-report measures for children with Osteogenesis Imperfecta(OI): a preliminary look

Maureen Donohoe¹, Cristina McGreal², Kenneth Rogers¹, Richard Kruse¹, Jeanne Franzone¹

¹Nemours Children's Health- Delaware, Wilmington, USA. ²Nemours Children's Health- Delaware, wilmington, USA

ABSTRACT

OBJECTIVES: To assess impact of pandemic-related social distancing requirements on children with OI using PROMIS scores collected at 3 timepoints: pre-pandemic, during pandemic-related social distancing, and after pandemic restrictions are relaxed

Since March, 2020 through the present, there has been a global pandemic taking place. Children in the United States of America often had modifications to their educational process through virtual learning and hybrid learning during the 2020/2021 school year. OI children lost the opportunity for regular exercise as well as in person therapy services. Little research looking at children's change from full time school to a virtual or hybrid format and impacts on health measures. .Based on social distancing standards, it is felt some scores would change during this period and hopefully return to baseline with return to activity.

METHODS: PROMIS surveys given at Nemours include upper extremity function, physical activity, anxiety, depression, fatigue, and social relationships, and pain interference

FMS scores define mild, moderate, and severe mobility function.

Individuals who had parent report surveys within a year of 3/2020, and two subsequent studies performed during social distancing protocols. Individuals who were 5 at first test and not over 17 at last test were included.

RESULTS: 11 individuals met criteria, 4 mild, 2 moderate, and 5 severe. 54% decreased functional scores, 72% has less anxiety and depression with improved peer relationships, 81% fatigue decreased. 54% pain interference increased.

CONCLUSION: Despite being a small study, it reflected better mental health and peer relationships than the typical population during this time. Functional scores regressed when severely involved. Depression increased in the moderate group. Virtual school had a more positive impact on the most severely involved. It may be due to reduced daily stressors of mobilizing out of the home.

P64

'In-Out-In' K-wires sliding technics in severe tibial deformities of osteogenesis imperfecta

Tristan Langlais, Georges Finidori, Marine de Tienda, Stéphanie Pannier, Mathilde Gaume, Zagorka Pejcin
Necker, Paris, France

ABSTRACT

OBJECTIVES: Severe infant osteogenesis imperfecta requires osteosynthesis. Intramedullary tibia's osteosynthesis is a technical challenge given the deformity and the medullar canal's narrowness. We describe an extramedullary technique: 'In-Out-In' K-wires sliding.

METHODS: We performed an anteromedial diaphysis approach. The periosteum was released while preserving its posterior vascular attachments. To obtain a straight leg, we did numerous osteotomies as many times as necessary. K-wires ('In') were introduced into the proximal epiphysis, and the medial malleolus ('Out') bordered the cortical and ('In') reach their opposite metaphysis. All tibial fragments were strapped along wires with a nonabsorbable mono- filament suture composed of the long-chain aliphatic polymers Nylon USP 1 (United States Pharmacopeia). We threaded the needle flush with the bone through the posterior periosteum. K-wires were cut, curved and impacted at their respective epiphysis ends to allow a telescopic effect. All tibial fragments are strapped on K-wires, and the periosteum was

sutured over it. Our inclusion criteria were children with osteogenesis imperfecta children with severe primary osteogenesis imperfecta type 3 following the new Sillence classification and operated before 6 years old whose verticalization was impossible.

RESULTS: Seven patients (11 tibias) are included (2006–2016) with a mean surgery's age of 3.3 ± 1.1 years old. All patients received intravenous bisphosphonates preoperatively. The follow-up was 6.1 ± 2.7 years. All patients could stand up with supports, and the flexion deformity correction was $46.7 \pm 14.2^\circ$. Osteosynthesis was changed in nine tibias for the arrest of telescoping with flexion deformity recurrence and meantime first session-revision was 3.8 ± 1.7 years. At revision, K-wires overlap had decreased by $55 \pm 23\%$. Including all surgeries, three distal K-wires migrations were observed, and the number of surgical procedures was 2.5/tibia. No growth arrest and other complications reported.

CONCLUSION: In-Out-In' K-wires sliding can be considered in select cases where the absence of a medullary canal prevents the insertion of intramedullary rod or as a salvage or alternative procedure mode of fixation. It can perform in severe infant osteogenesis imperfecta under 6 years old with few complications and good survival time.

P65

What's in a Name? Prevalence of Metaphyseal Fractures in Children with Osteogenesis Imperfecta in the First Two Years of Life

Ella Riley¹, Sara Mohammed², Paul Arundel², Nicholas Bishop², Amaka Offiah²

¹University of Sheffield, Sheffield, United Kingdom. ²Sheffield Children's Hospital, Sheffield, United Kingdom

ABSTRACT

OBJECTIVES: Metaphyseal fractures otherwise called classic metaphyseal lesions (CMLs) are highly suggestive of inflicted injury. Osteogenesis imperfecta (OI) is often suggested as a differential diagnosis in infants presenting with unexplained fracture(s). It is important to be confident in differentiating OI from physical abuse when fractures are otherwise unexplained. To our knowledge, there have been no large-scale studies looking at this issue. This study aims to assess the prevalence of CMLs in children with OI during the first two years of life.

METHODS: Retrospective review of case notes and radiographs of children with OI, aged 0-2 years between 1st January 2010 and 31st December 2021. The metabolic bone team (NJB, PA) at Sheffield Children's Hospital produced a list of patients attending the OI clinic and radiographs were obtained from a search of the Hospital's digital imaging system. Images and reports were analysed by a medical student (ER) alongside a paediatric radiologist with over 20 years' experience (ACO). The site and type of fracture were recorded along with other radiological features of OI such as Wormian bones. Descriptive statistics were used to analyse the results.

RESULTS: The total number of children attending the OI clinic was 536; 424 were excluded as they were either older than 2 years (250), found not to have OI (63) or did not have relevant imaging (111). The 112 recruited patients had a total of 3,192 images (1,997 images < 1 year and 1,195 1-2 years). A total of 64 metadiaphyseal fractures were identified but only a single fracture initially suggestive of a CML. However, follow-up imaging revealed metadiaphyseal extension of the fracture line, not typical of CMLs. Furthermore, although OI was confirmed, the child and an older sibling are being investigated for abuse.

CONCLUSION: The absence of CMLs detected in a relatively large cohort of children with confirmed OI suggests that OI is not causative for CMLs; unfortunately, infants and young children with OI may still be abused. Metadiaphyseal fractures, reflecting fragility, are more common in OI; distinction should be made between "metaphyseal" and "metadiaphyseal" fractures to facilitate clinical decision-making.

P66

Evidence for Metaphyseal Fractures Typical of Abuse in Osteogenesis Imperfecta: A Systematic Review

Ella Riley¹, Michael Paddock², Joanna Fairhurst³, Kath Halliday⁴, Annmarie Jeanes⁵, Karl Johnson⁶, Amaka Offiah⁷

¹University of Sheffield, Sheffield, United Kingdom. ²Barnsley Hospital NHS Foundation Trust, Barnsley, United Kingdom. ³University Hospital Southampton, Southampton, United Kingdom. ⁴Nottingham University Hospital, Nottingham, United Kingdom. ⁵Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom. ⁶Birmingham Women's and Children's NHS Foundation Trust, Birmingham, United Kingdom. ⁷Sheffield Children's Hospital, Sheffield, United Kingdom

ABSTRACT

OBJECTIVE: To search for evidence of metaphyseal fractures (also known as classic metaphyseal lesions, CMLs) in children aged 0 to 2 years with osteogenesis imperfecta (OI) to differentiate from inflicted injury in infants with unexplained fractures.

METHODS: A systematic review of Medline, Cinahl and Web of Science was conducted. Inclusion criteria: studies of children < 2 years of age with OI which report the number of CMLs. Studies were excluded in which the full article was not retrievable, not in English or the authors neither define nor illustrate what they mean by "metaphyseal fracture". All radiographs included of "metaphyseal" fractures were independently reviewed by 6 paediatric radiologists as to the quality of the illustrated images and whether a CML was present. The quality of the included papers will be assessed using the QUADAS-2 tool.

RESULTS: A total of 256 articles were retrieved with 81 duplicates. There were 175 articles screened based on abstract and title and 151 excluded. A total of 26 articles were reviewed with a hand search of the references adding 2 articles. Only 4 articles were included. Article 1 reviewed 41 children with OI and found 7 with "metaphyseal" fractures, aged between 1 day and 3 years. Article 2 reported 3 "metaphyseal" fractures in a 16-month-old male. Despite a diagnosis of type IV OI (not genetically confirmed), there remained concerns about physical abuse. Article 3 reported a 7-month-old female who presented with multiple fractures including 2 "corner" fractures. The child was suspected both to have OI and to have been abused. Article 4 reported a pair of siblings with "metaphyseal" fractures who both had a FKBP10 genetic mutation causing type XI OI. The 4 studies included 8 images which the authors purport to show 9 "metaphyseal" fractures. Of these, 3 images were considered of diagnostic quality, and none were classed as CMLs by all 6 radiologists.

CONCLUSION: There is limited scientific evidence that OI predisposes infants and young children to CMLs. Physical abuse should always be considered as a differential diagnosis in infants and young children with CMLs, even in the context of confirmed OI.

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Bone Mass, Density, Geometry and Stress-Strain Index in Adults with Osteogenesis Imperfecta Type I, and their Associations with Physical Activity and Muscle Function Parameters

Marie Coussens¹, Bruno Lapauw^{2,3,4}, Stefan Goemaere^{2,4}, Charlotte Verroken^{2,4}, Inge De Wandele⁵, Fransiska Malfait^{4,5}, Thibério Banica^{2,3}, Patrick Calders¹

¹Department of Rehabilitation Sciences and Physiotherapy, Ghent University, Ghent, Belgium. ²Unit for Osteoporosis and Metabolic Bone Diseases, Ghent University Hospital, Ghent, Belgium. ³Department of Internal Medicine and Paediatrics, Ghent University, Ghent, Belgium. ⁴Reference Centre for Rare Bone, Calcium and Phosphate Disorders, Ghent University Hospital, Ghent, Belgium. ⁵Centre for Medical Genetics, Ghent University Hospital, Ghent, Belgium

ABSTRACT

OBJECTIVES: To assess bone parameters in adults with osteogenesis imperfecta (OI) type I, and their relationship with physical activity and muscle function parameters in comparison with controls.

METHODS: A total of 27 (15 women, 12 men) adults with OI type I and 27 healthy age- and gender matched controls, with mean age 45 years (range 18-72), were included. Peripheral quantitative computed tomography at tibia and radius was performed to assess trabecular (4% site) and cortical bone parameters (66% site). Physical activity (step count) was assessed by accelerometry, muscle function parameters by Leonardo mechanography (single two-legged jump – peak power) and hand grip dynamometry (maximal hand grip strength).

RESULTS: Adults with OI type I had significantly lower step count (43% difference, $p=0.001$), and for the same height and weight, no significantly different muscle function parameters (peak power: $p=0.368$, maximal hand grip strength: $p=0.736$), but significantly lower trabecular (tibia: 36% difference, $p<0.001$; radius: 34% difference, $p=0.034$) and cortical (tibia: 19% difference, $p=0.007$; radius: 26% difference, $p<0.001$) bone mineral content (BMC), thinner cortices (tibia: 21% difference, $p=0.001$; radius: 28% difference, $p<0.001$) and lower polar stress-strain index (SSIp; tibia: 26% difference $p<0.001$; radius: 30% difference, $p=0.001$), and higher cortical bone mineral density (tibia: 2% difference, $p=0.087$; radius: 2% difference, $p=0.008$), in comparison with controls.

Peak power was positively associated with cortical BMC at the tibia ($p<0.001$), and maximal hand grip strength with SSIP at the radius ($p=0.023$) in the control group, but not in the OI type I group ($p=0.173$ and $p=0.951$, respectively) (difference in associations: $p=0.045$ and $p=0.023$, respectively). No other statistically significant differences in associations between bone and muscle function parameters, or step count were found in the OI type I versus control group. In both groups, no associations were found with step count.

CONCLUSION: Adults with OI type I have smaller bones, lower trabecular bone mass, lower estimates of bone strength, but higher cortical density in comparison with controls. Our results suggest that the biomechanical muscle-bone relationship in adults with OI type I might be disturbed, and that step count is not a good proxy for bone mechanical loading through physical activity.

P68

Typing with OI Type 5

Zoe Bowman Bayles, Tracy Connolly, Catherine DeVile

Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom

ABSTRACT

BACKGROUND: Osteogenesis Imperfecta type 5 is a moderate form of the condition, characterised by bone fragility, mineralised interosseous membranes of the forearm and lower leg, hyperplastic callus formation and dislocation of the radial head.

A distinct feature of OI type 5 is limitation in the range of pronation/supination in one or both forearms, associated with calcification of the interosseous membrane. Pronation and supination of the forearm occurs within a wide variety of functional day to day tasks such as cutlery use, recording work in school and personal hygiene.

PRESENTING PROBLEM: 17 year old female reported ongoing pain in left forearm. No historical upper limb fractures. Previous inability to flex left elbow which resolved and restrictions of pronation and supination but remained functional. Priority concern identified was using a keyboard to record academic work, of increasing concern in light of starting university.

CLINICAL MANAGEMENT: Within the OI MDT clinic, x-rays of the hand, wrist and forearm were reviewed and showed progression of interosseous membrane calcification bilaterally, no radial head dislocation & bone age was significantly advanced.

Active and passive range of motion was measured using goniometry and demonstrated significant restrictions in forearm range of motion.

To observe and measure typing speed two subtests were completed from the Detailed Assessment of Speed of Handwriting. A young person should be able to type the alphabet and a copy a sentence at a speed

similar to handwriting rates expected for their age level. The young person scored above average in both tests.

OT gained consent and contacted REMAP, a charitable company, to discuss collaborative working and to make a bespoke keyboard to reduce her discomfort when recording longer pieces of work.

DISCUSSION: Six months on, she reported a reduction in pain and stiffness. Furthermore, she had been able to develop her own problem-solving strategies to adapt to the reduced movement in her forearms. Video analysis of typing demonstrated a unique biomechanical compensatory approach which facilitated an individualised approach to efficient and pain-free typing without the need for bespoke equipment. Further study is required to know more about function despite restrictions in forearm range.

P69

Gene Expression Profiling of Fetal Mesenchymal Stem Cells during Osteogenic Differentiation

Emine Begüm Genç-Öncül, Yuk Kit Lor, Åsa Ekblad-Nordberg, Annika Goos, Lilian Walther-Jallow, Cecilia Götherström
Karolinska Institute, Stockholm, Sweden

ABSTRACT

OBJECTIVES: Severe Osteogenesis Imperfecta (OI) is a debilitating genetic disorder leading to multiple fractures, grave handicap, and pain. Mesenchymal stem cells (MSCs) is a good candidate to treat OI, leading to reduction of fractures and increase of lengthwise growth. Fetal MSCs (fMSCs) have more potential and differentiate much more readily into bone than their adult counterparts and are currently being investigated in the BOOSTB4 clinical trial as a treatment for OI. The bone differentiation assay is currently being used as a release assay for the fMSC drug product. To better predict fMSC potency, the assay needs to be further developed, to increase accuracy and control for variability. To accomplish this, we have investigated fMSCs gene expression profile during induction with bone differentiating media with the aim to find specific markers that could be early predictors of bone differentiation capacity in the fMSCs.

METHODS: Fetal MSCs were isolated from four different donors and were expanded up to passage 5. The fMSCs were differentiated into bone using osteogenic medium (BONE-group) and growth medium (CTRL-group). RNA isolations were performed on Day (D)0, D1, D2, D3, D4 and D10, D17 in both the BONE and the CTRL group. The most significant genes (padj value <0.05 and log₂ fc >0) ranked by, for early stage (D0-D4). Gene ontology analysis was performed.

RESULTS: A total of 1535 (D0 vs D2), 2745 (D0 vs D3) and 4286 (D0 vs D4), genes were upregulated during osteogenic differentiation from D0 to D4, respectively. We discovered differentially expressed genes that have not yet been described in the context of osteogenesis, which includes the genes that were the most significantly changed.

CONCLUSION: Our findings of differential expressed genes and significantly changed pathways provide new insight into osteogenic differentiation of fMSC, and may improve manufacturing of MSCs, and treatments using MSCs in osteogenic-related diseases.

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Effect of Blood Flow Restriction Training on Bone, Muscle, Pain, and Fatigue in Adults with Osteogenesis Imperfecta type I: a Protocol Proposal of a Randomized Controlled Clinical Trial

Marie Coussens¹, Bruno Lapauw^{2,3,4}, Charlotte Verroken^{2,3,4}, Inge De Wandele⁵, Fransiska Malfait^{4,5}, Lies Rombaut⁵, Paul Coucke⁵, Patrick Calders¹

¹Department of Rehabilitation Sciences and Physiotherapy, Ghent University, Ghent, Belgium. ²Unit for Osteoporosis and Metabolic Bone Diseases, Ghent University Hospital, Ghent, Belgium. ³Department of Internal Medicine and Paediatrics, Ghent University, Ghent, Belgium. ⁴Reference Centre for Rare Bone, Calcium and Phosphate Disorders, Ghent University Hospital, Ghent, Belgium. ⁵Centre for Medical Genetics, Ghent University Hospital, Ghent, Belgium

ABSTRACT

BACKGROUND: Disturbed muscle (strength, mass, and metabolism) and bone (mass, geometry, strength, microarchitecture, and metabolism) parameters have been shown in osteogenesis imperfecta (OI). However, physiotherapy targeting these parameters, including high-impact or high-intensity exercises, entails high fracture risk. We hypothesize that low-intensity training with blood flow restriction (BFR), which has proven to safely benefit bone health and muscle growth in several healthy and clinical adult populations, could safely target muscle and bone parameters in OI.

OBJECTIVES: To evaluate the effect of low-intensity muscle strength training (LI-MST) with BFR on bone and muscle parameters, pain, and fatigue in adults with OI type I.

METHODS: First, questionnaires and interviews will evaluate feasibility, acceptability, and safety (symptoms and adverse events) of LI-MST with BFR in 10 adults (18–40 years old, 5 women, 5 men) with OI type I, in a pilot study at Ghent University Hospital (Belgium) in September 2022.

In the subsequent randomized controlled clinical trial (RCT), based on power calculations (effect size estimate $f=0.4$, with 95% power, $\alpha=0.05$ and 20% drop-out), we aim to recruit 75 adult men and women with OI type I, aged between 18 and 40 years old, in several countries. Exclusion criteria include pregnancy or <6 months postpartum, deep vein thrombosis, acute fractures, oedema or recent surgery in arms or legs, and cardiovascular, respiratory or neuromuscular diseases or other contraindications to perform exercise.

Participants will be randomly assigned (block randomisation) into LI-MST with BFR, LI-MST without BFR, or a control group (standard care). The exercise group will perform home-based exercises 2–3 times a week for 12 weeks. Training intensity will be set at 20% of 1-repetition maximum (1RM) and reset every 4 weeks for increasing intensity. In the BFR group, pressure will be applied by an inflatable cuff at the most proximal site of the arm or leg, inducing venous occlusion and partial arterial occlusion. Muscle and bone parameters will be evaluated by peripheral quantitative tomography, dual-energy x-ray absorptiometry, 1RM measurements, and blood samples, while pain and fatigue will be measured by questionnaires, at baseline, after 12 weeks (intervention), 6 months (follow-up 1) and 12 months (follow-up 2).

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Muscle Function Parameters in Adults with Osteogenesis Imperfecta type I: Preliminary Results

Marie Coussens¹, Fransiska Malfait^{2,3}, Inge De Wandele³, Patrick Calders¹, Verity Pacey⁴

¹Department of Rehabilitation Sciences and Physiotherapy, Ghent University, Ghent, Belgium. ²Reference Centre for Rare Bone, Calcium and Phosphate Disorders, Ghent University Hospital, Ghent, Belgium. ³Centre for Medical Genetics, Ghent University Hospital, Ghent, Belgium. ⁴Department of Health Sciences, Macquarie University, Sydney, Australia

ABSTRACT

OBJECTIVES: To assess muscle function parameters in adults with osteogenesis imperfecta (OI) type I.

METHODS: A total of 44 (28 women, 16 men) adults with OI type I and 57 (31 women, 26 men) healthy controls were included, with mean age 44 (range 18-76) and 42 years (range 18-71), respectively. Anthropometrics, self-reported fractures, orthopaedic surgeries, and painful body surface (Margolis diagram) were recorded. Muscle function parameters were assessed by the 30 seconds chair rise test (30sCRT), hand grip dynamometry (bilateral maximal hand grip strength, hand grip endurance strength of the dominant hand), hand held dynamometry (maximal isometric strength of dominant hip flexors, ankle dorsiflexors, and shoulder abductors), posture maintenance tests (static endurance strength of dominant hip flexors, bilateral shoulder abductors, wall sit), six-minute walking test (6MWT), and respiratory measurements (maximal inspiratory and expiratory pressure). Statistical analyses were done by linear mixed models, with adjustment for height, weight and gender, or by Fisher exact tests.

RESULTS: Adults with OI type I had, in comparison with controls, significantly lower height (6% difference, $p<0.001$), higher body mass index (8% difference, $p=0.021$), more self-reported fractures ($p<0.001$) and orthopaedic surgeries ($p=0.010$), higher painful body surface (89% difference, $p<0.001$), less rises in the 30sCRT (21% difference, $p<0.001$), lower maximal hand grip strength (23-26% difference, $p\leq 0.045$), lower maximal isometric strength of the hip abductors (28% difference, $p<0.001$), ankle dorsiflexors (25% difference, $p=0.015$), and shoulder abductors (41% difference, $p<0.001$), lower static endurance strength of the hip flexors (34% difference, $p<0.001$), shoulder abductors (21% difference, $p<0.001$) and during wall sit (38% difference, $p=0.008$), and a lower 6MWT distance (22% difference, $p<0.001$). No significant differences were found regarding weight ($p=0.416$), respiratory measurements (maximal inspiratory pressure: $p=0.343$, maximal expiratory pressure: $p=0.418$), and hand grip endurance strength ($p=0.693$) between the OI type I and control group.

CONCLUSIONS: Adults with OI type I have generalized lower peripheral skeletal muscle function parameters in comparison with controls, whereas respiratory muscle strength is similar in comparison with controls. Physiotherapy should target these parameters through muscle strengthening, but future research is needed to evaluate its safety in adults with OI type I.

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WNT1-related osteogenesis imperfecta Type 15 and intramembranous calcification: subtle skull vault mineralisation defect only evident on 3D CT head

Christine P Burren^{1,2}, Sarah F Smithson^{1,2}, Julia James³, Amaka Offiah^{4,5}

¹University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, United Kingdom. ²University of Bristol, Bristol, United Kingdom. ³Torbay and South Devon NHS Foundation Trust, Torquay, United Kingdom. ⁴University of Sheffield, Sheffield, United Kingdom. ⁵Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom

ABSTRACT

BACKGROUND: Osteogenesis imperfecta (OI) incorporates classical subtypes affecting collagen assembly and rarer subtypes affecting bone formation. WNT1, crucial for preosteoblast activity, was associated

initially with osteoporosis then with OI type 15^[1]; phenotype involves multiple fractures, progressive deformity, short stature, variably blue sclera. Radiographic changes may be underappreciated in ultrarare subtypes^[2].

PRESENTING PROBLEM: Presented aged 6 weeks with right femur fracture, no clear trauma history. Mild antenatal femoral shortening at 32/40 (~10th centile); mother had 3 forearm fractures aged 4, 10 and 13 years and osteoporosis affected maternal grandmother and great aunt. Clinical examination: large anterior fontanelle, subtly blue sclerae, no ligamentous laxity. Skeletal survey disclosed multiple older fractures: left femur, bilateral humeral, clavicular, ribs and 1st metatarsal metadiaphyseal corner fracture. Skull vault normal on radiographs (normal mineralisation, no Wormian bones), whereas CT 3D reconstruction revealed patchy calvarial mineralisation defects.

CLINICAL MANAGEMENT: At 6 weeks, OI was diagnosed clinically (substantiated by clinical, antenatal and maternal history features and abnormal calvarial appearance) and zoledronic acid commenced. Initial opinions differed on CT interpretation – potentially voluming effect from CT software Hounsfield settings. Re-analysis against contemporaneous CT scans (4 infants, same machine, same Hounsfield settings) confirmed patient specific abnormality indicating reduced calvarial mineralisation. Whole Exome Sequencing identified a pathogenic frameshift variant c.287_300del,p.(Gln96fs) and a missense variant c.688C>T,p.(Arg230Cys) in WNT1. Subsequently, one fragility humeral fracture (9mo), 3 vertebral fractures, no platyspondyly or scoliosis (radiology monitoring 12mo); linear growth 2nd centile, steady developmental progress, and no deformities at 16mo.

DISCUSSION: Reduced calvarial mineralisation on conventional radiography is reported in 2 infants^[1] but more subtle in this infant and only evident on CT 3D reconstruction. WNT signalling occurs in intramembranous calcification. Compound heterozygous WNT1 pathogenic variants in this infant potentially underpin the calvarial calcification defects, which may represent a subtle but characteristic component of OI type 15. Whilst CT does not form routine assessment of suspected OI, where already performed as part of routine workup of unexplained injuries, it is valuable to assess for skull vault calcification abnormalities.

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P73

The methodological approaches used to understand the psychosocial experiences of parents of children with osteogenesis imperfecta: A review

Yu Chen Shi^{1,2}, Sofia Addab², Argerie Tsimicalis^{2,1}, Reggie Charles Hamdy^{2,1}

¹McGill University, Montreal, Canada. ²Shriners Hospitals for Children, Montreal, Canada

ABSTRACT

OBJECTIVES: Parental coping is important for the course of rare genetic diseases. The objective of this narrative literature review is to identify the methodological approaches used to understand the psychosocial experiences of parents of children diagnosed with OI.

METHODS: Relevant publications were identified through a search of the literature in three electronic databases: MEDLINE, PsycInfo, and CINAHL. No timeframe restrictions were used. Papers must be written in English. Search results from the three databases were imported into Covidence for deduplication and screening. Only primary papers were retained for full-text review. Backward citation searching was then conducted. Study characteristics were tabulated for data abstraction and descriptive synthesis.

RESULTS: Of the 50 studies screened, 6 were retained. The first paper to use an instrument to measure parental psychosocial status was published in 2003. Overall, 7 different tools were used in the 6 retained studies to understand the experiences of parents of children with OI. These tools can be divided into 2 categories: ones that assess

psychologic experiences such as stress, depression and coping, and ones that assess quality of life. Only one tool, the WHOQOL-BREF questionnaire, was used in more than one study.

CONCLUSION: Efforts to understand parental experiences of OI have been ongoing. However, there is a paucity of information on the subject and an inconsistent use of many instruments that yield different outcomes, such that comparison between the results of the studies is very difficult. Though the OI/ECE questionnaire was developed in 2016 to evaluate the impact of OI on the lives of patients and their families, no other studies have used it to date. The Key4OI group has published an article listing the recommended measurement tools for various outcomes in patients with OI. A similar consensus is needed to fully capture the experience of the parents of children with OI.

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The Osteogenesis Imperfecta Variant Database: current state

Sonna Stolk¹, Lidiia Zhytnik^{2,3,4}, Taco van Welzenis⁵, E Marelise W Eekhoff^{6,3}, Lisanne E Wisse^{2,3}, Raymond Dalgleish⁷, Alessandra Maugeri¹, Gerard Pals^{2,3}, **Dimitra Michal**^{2,3}

¹Department of Human Genetics, Amsterdam Genome Diagnostics (AGDx), Amsterdam UMC, Amsterdam, Netherlands. ²Department of Human Genetics, Center for Connective Tissue Diseases, Amsterdam UMC, Amsterdam, Netherlands. ³Amsterdam Movement Sciences, Amsterdam, Netherlands. ⁴Department of Traumatology and Orthopedics, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia. ⁵Osteogenesis Imperfecta Federation Europe, Heffen, Belgium. ⁶Department of Internal Medicine Section Endocrinology, Amsterdam UMC, Amsterdam, Netherlands. ⁷Department of Genetics and Genome Biology, University of Leicester, Leicester, United Kingdom

ABSTRACT

OBJECTIVE: The Osteogenesis Imperfecta Variant Database (OIVD) contains comprehensive information on variants, their pathogenicity, and patients' phenotypes. Submission of newly found variants to OIVD will further enhance its significance for the OI community.

The database was created around 1984 and is widely consulted for OI gene diagnoses and numerous research projects. In 2008 the database migrated to the Leiden Open Variation Database (LOVD), supported initially by the EC GEN2PHEN project. The current OIVD includes variants for 25 genes for OI and overlapping disorders. The database is recognized as a powerful tool for genetic diagnosis, prediction of disease progression, genotype-phenotype correlations, and translational and clinical research. Recently, the main curation of the database was transferred to Amsterdam UMC. We encourage variant submission to OIVD to ensure consolidation and harmonization in OI variant interpretation.

METHODS: Variants, published in journals, should be submitted to OIVD. Anybody can become a submitter (https://databases.lovd.nl/shared/docs/LOVD3_submit.pdf). Variant reporting follows current standards (mandatory transcript identifier and use of the HGVS variant nomenclature guidelines), pathogenicity assessment uses the ACMG guidelines, and correct OI clinical types are reported. These measures apply to variants submitted both directly to LOVD-OI and to those from the literature added by the curators. All data are checked and verified by the curators of the database.

All OI variant information can be found at <https://lovd.nl/OI-genes>.

RESULTS: OIVD contains approximately 3250 unique OI variants in 6290 patients, with a complete coverage of variants till 2018. Completing and updating the database with published variants (2019-current) is being reinitiated by Amsterdam UMC. Currently, missing OI variants from 2019-2020, are being submitted, including 930 variants from the AGDx.

CONCLUSION: OIVD is the most comprehensive database of OI genetic variants and patient phenotypic data but few updates have been made since 2018. We strongly encourage our colleagues to submit their (un)published variants and the database is open for submissions.

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Engaging the osteogenesis imperfecta (OI) community in patient centered outcomes research

Tracy Hart¹, Erika Carter¹, Michael Stewart¹, Austin Gillies², Elmer Rajah², **Laura L. Tosi**^{2,3}

¹Osteogenesis Imperfecta Foundation, Gaithersburg, MD, USA. ²Children's National Hospital, Washington, DC, USA. ³The George Washington School of Medicine and Health Sciences, Washington, DC, USA

ABSTRACT

OBJECTIVES: Patient engagement in the research process is essential to elucidating the priority issues of the osteogenesis imperfecta (OI) community. Including patients and caregivers builds trust and creates implementable information for improving clinical care. We report on a recent Patient Centered Outcomes Research Institute (PCORI) award to the OI Foundation (OIF) focused on engaging more OI patients, caregivers, clinicians, and researchers in patient centered outcomes research (PCOR), and preparing them for future comparative effectiveness research (CER).

METHODS: Using a virtual meeting strategy to introduce PCOR, the OIF established a PCOR Advisory Board and Communication and Education Committees primarily populated by members of the OI community, employing six strategies to educate stakeholders: 1) Broaden the range of OI community stakeholders trained in PCOR, 2) Include PCOR education in all new and traditional advocacy/educational events 3) Develop a PCOR Communications Strategic Plan 4) Expand OIF communication with OI clinics that were not actively engaged with the Foundation. 5) Develop an OI-specific PCOR toolkit 6) Leverage the OIF Registry to engage the OI community in developing its own answers.

RESULTS: Virtual programming secured significant participation from individuals who had not previously been involved with the Foundation. The 2020 National Meeting improved from 600 to 900 registrations, with over 400 new email contacts. Educational efforts for clinicians who treat OI were expanded by adding a bi-annual virtual town hall, with 60-90 attendees for each of the first 3 events. Expanded communication led to increased followers across social media over 2 years - Facebook: 13,663, (+24%), Twitter: 2,632 (+8%), and Instagram 1,468 (+297%). The OI-specific PCOR Toolkit (<https://oif.org/research/pcor/>), containing 10 video PCOR teaching modules and manuscripts focused on OI patient reported outcomes, has been viewed over 500 times. The OIF has just completed its third COVID-19 survey with participation of 400-650 individuals each time.

CONCLUSION: The OIF is now ensuring that the "patient voice" is included in all OI research and advocacy activities. The long-term goal is to engage the OI community in future studies to evaluate the comparative effectiveness of diagnostic and treatment strategies.

P76

5-years experience of telescopic rods surgery for osteogenesis imperfecta patients in Russia

Alexey Rykunov, Natalia Belova, Vladimir Kotov, Ivan Ledenev
GMS Clinic, Moscow, Russian Federation

ABSTRACT

BACKGROUND: over decades since invention of telescoping rod no any kind of this implants were available in Russia. Surgical treatment for prevention of fracture and deformity correction in patients with osteogenesis imperfecta was performed with traditional orthopaedic devices (plates, K-wires, Ilizarov's fixators, titanium elastic nails). Such surgical treatment in most cases did not prevent further deformity or

caused long immobilization after, so increased reoperation rate and decreased mobility of patients.

PRESENTING PROBLEM: share clinical results of telescoping rod surgeries in OI patients in Russia

CLINICAL MANAGEMENT: since September 2017 till April 2022 at our institution 200 surgeries with telescoping rod insertion in 77 patients (age 2.5 to 19 y) were performed. Male: female ratio was 1:1.2/ 123 femurs, 70 tibias and 7 humerus surgeries were done. In 5 cases we used Bailey-Dubow rods, other 195 cases were treated with Fassier-Duval rods. All patients had regular cyclic intravenous bisphosphonate infusions.

RESULTS: stay at the hospital after surgery was 2-7 days (average 3,3 days). Duration of cast immobilization was 4 -8 weeks (average 6 weeks). The patients had a mean satisfaction score of 8,8 (range of 5-10 from total 10 score).

Surgical treatment of OI patients with telescoping rods significantly increases patient satisfaction, requires short immobilization after surgery therefore increases quality of life

P77

The GOSH Osteogenesis Imperfecta Team: Taking a Psychosocial Approach

Charlotte Barran, Anita Freeman, Mark Heathfield, Catherine DeVile

Great Ormond Street Hospital for Children, London, United Kingdom

ABSTRACT

OBJECTIVES: This is a brief introduction to the psychology and social work services at Great Ormond Street Hospital for Children (GOSH) and how we work with the Osteogenesis Imperfecta (OI) Multi-Disciplinary Team (MDT) to understand and respond to psychosocial issues for families affected by mild, moderate and severe OI.

METHODS: An explanation will be provided of how referrals are made and statistics on the quantity and nature of referrals to GOSH OI psychology and social work services for twelve months from 2021 to 2022. We will outline statistical information on referrals made to local authority social work teams and psychological support provided within OI service and referrals to local mental health services.

We outline our multi-disciplinary approach, explaining the teams integrated working together to support families, including monthly MDT psychosocial meetings. We describe how the team interacts, liaises and engages with local services to provide the best support for our patients – for example arranging and attending MDTs, professionals' meetings, Child in Need (CIN) and Child Protection (CP) meetings

We describe examples of collaborative working between psychology and social work, meeting with families together to take a holistic approach to providing support

RESULTS: We explain highlights of our bespoke psychosocial approach and how we feel it is an effective way to support families in a collaborative and open way, including how we have been able to adapt positively to the SARS-CoV-2 (COVID-19) pandemic restrictions. We will talk about resource constraints in the community to provide appropriate support

CONCLUSION: Results showed the need for Psychosocial support within our cohort of families and patients has increased across all severities of patients with OI during the last year.

CONFLICTS OF INTEREST: none

P78

A feasibility study exploring the suitability of the Bayley Scale of Infant and Toddler Development in assessing children from 16 days to 42 months with Osteogenesis Imperfecta who are under the care of the Metabolic Bone Team at Sheffield Children's NHS Foundation Trust

Caroline Marr¹, Claire Hill¹, Rebecca Jones^{1,2}

¹Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom.

²The University of Sheffield, Sheffield, United Kingdom

ABSTRACT

Osteogenesis imperfecta (OI) is a rare genetic disorder that affects collagen biosynthesis. Severity of OI is variable, with all types recognised to have a high burden of disease. Prominent features include fractures, bony deformity, and developmental delay. Within the UK there is no consensus on how to screen for and monitor developmental in this patient group.

OBJECTIVES: The primary objective was to assess the suitability of the Bayley Scale of Infant and Toddler Development (BSITD) in children with OI. The secondary objectives were to investigate; recruitment strategy, rate, and retention; suitability and characteristics of the BSITD in comparison to the Ages and Stages (A&S); determine the acceptability of the investigational techniques, data collection and management; review timescale and cost.

METHOD: Participants were purposefully sampled from a cohort of children, with OI, who were under the age of 30 months and attended Sheffield Children's Hospital. 2 assessments, at least 6 months apart were completed with each participant. Each assessment included physiotherapy review; assessment of physical function using the Brief Assessment of Motor Function; BSITD and the A&S.

RESULTS: 21 participants were recruited: 15 had mild, 3 moderate and 3 severe OI. 3 participants were lost to follow up. All assessments were accepted by the participants and parents. All BSITD assessments were fully completed, with the observation that most of the children became tired towards the end of the assessment. Within the BSITD assessment children recurrently failed to; ascending and descending the stairs; use scissors; demonstrate representation play; retrieving objects through an open-ended box. Developmental delay was documented across all types when using the BSITD and the A&S. Delay in gross motor attainment was most frequently observed in both the BSITD and A&S. Both the BSITD, and A&S gave clinically relevant information. Comparison of results gained from the BSITD and A&S were similar in the motor section. There were differences in the cognitive and language subsections, with the BSITD suggesting more delay than the A&S.

CONCLUSION: The study suggests that the BSITD is an acceptable assessment to use in children with OI and may provide a more in-depth review of language and cognitive development.

P79

Upper limb function in osteogenesis imperfecta: a scoping review

JASMINE ROCCI¹, Reggie Hamdy^{2,1}, Argerie Tsimicalis^{2,1}

¹McGill University, Montreal, QC, Canada. ²Shriners Hospital for Children, Montreal, QC, Canada

ABSTRACT

OBJECTIVES: Osteogenesis imperfecta (OI) is an inherited disorder characterized by mutations of collagen type I. This defect leads to abnormal bone formation and growth. While deformities of the upper limbs seem to occur less frequently than those of the lower limbs, upper limb function is a greater predictor of quality of life. In evaluating functional outcomes of pediatric patients, those with more severe upper limb deformities have significantly impaired function in activities of daily living. Yet, despite this known functional impact, little has been done to define management guidelines for upper extremity

malformations in OI patients. Hence, the purpose of this review was to describe the existing methods to upper limb malformation measurement and subsequent therapy to inform the creation of future guidelines.

METHODS: A scoping review was conducted following the Joanna Briggs Institute (JBI) methodology. PubMed, Medline, and Cochrane Review, alongside the Google search engine, were searched using an inclusive list of keywords to focus on OI and upper limb function. Articles with only adult data (18-year-old patients or older) were excluded. There were no date or language restrictions. Methodology, study population, and other parameters consistent with the JBI criteria were extracted, along with descriptions of severity classifications and subsequent management guidelines. Data was analyzed with qualitative thematic analyses.

RESULT: Across all databases, the search yielded 63 results, 21 of which were included. Of those, 3 empirical studies (1 cohort and 2 cross-sectional), 11 case reports or case series, 3 reviews, and 4 expert-opinion-based studies (1 conference summary, 3 consensus statements) were included. Most frequently, upper limb function was not focused on as a primary outcome of the article, and limb function was inconsistently measured and valued leading to difficulty of comparison across studies.

CONCLUSIONS: There is a need for multicenter studies to better define upper limb function measurement as well as set guidelines for management of these deformities in children with OI.

P80

Using virtual communication for rapid dissemination of COVID-19 information to patients with osteogenesis imperfecta

Tracy Hart¹, Erika Carter¹, Elmer Rajah², Austin Gillies², Michael Stewart¹, **Laura L. Tosi^{2,3}**

¹Osteogenesis Imperfecta Foundation, Gaithersburg, MD, USA. ²Children's National Hospital, Washington, DC, USA. ³The George Washington University School of Medicine and Health Sciences, Washington, DC, USA

ABSTRACT

OBJECTIVES: When the COVID-19 pandemic arrived in the United States, the Osteogenesis Imperfecta Foundation (OIF) sought to provide relevant information about safety and wellbeing during the pandemic for over 25,000 individuals with osteogenesis imperfecta (OI) and their caregivers. This objective was particularly compelling because individuals with OI are believed to have a higher risk of severe COVID-19 infection due to impaired lung function. The Foundation expanded traditional dissemination methods, introducing novel approaches to engage patients with OI, and provide timely information on a variety of patient-identified concerns.

METHODS: The first step in the OIF's response to the COVID-19 pandemic was the formation of a COVID-19 Task Force – a multidisciplinary team of physicians, public health experts, patients, and other stakeholders who met monthly to help coordinate the OIF's engagement during the pandemic. The OIF administered a series of surveys for patients with OI and their caregivers to gauge community perspectives and field concerns about the pandemic. The results from these surveys were used to develop “community calls” for the OI community which covered topics including safety during COVID-19, orthopaedic care, mental and physical wellness, employment considerations, and the importance of vaccines. Community calls offered interactive engagement and unique opportunities for participants to access internationally recognized experts in different topic areas. These recorded webinars and other resources were then posted on the OIF website as part of a COVID-19 Toolkit, shared on social media, and published in the Breakthrough newsletter.

RESULTS: Results from COVID-19 surveys indicated significant concerns in the OI community about mental health, COVID-19 vaccine safety, and physical activity which guided OIF webinar topic selection. The COVID-19 Toolkit available on the OIF website has garnered over 2,500 unique visitors and the webinar recordings have more than 5,600

collective views. Moreover, approximately 50% of participants in virtual programs had never engaged with the OIF in the past.

CONCLUSION: The OIF's combined use of surveys and webinars alongside traditional methods of disseminating information demonstrates how patient-centered communication can be used to rapidly respond to patient needs during an emergency.

P81

Quality of life and coping strategies in adults with OI

Margarida Santos^{1,2}, Ana Gomes^{1,2}, **Ceú Barreiros^{3,4,5}**, Andreia Magalhães^{3,4}, André Travessa³, Patricia Dias³, Afonso Ferreira^{3,4}, Fatíma Godinho⁶, Fausto Pinto^{3,4}

¹Escola Superior de Tecnologia da Saúde do Instituto Politécnico de Lisboa, Lisboa, Portugal. ²Centro de Investigação em Ciências Psicológicas da Faculdade de Psicologia da Universidade de Lisboa, Lisboa, Portugal.

³Hospital de Stª Maria – Centro Hospitalar Universitário de Lisboa Norte, Lisboa, Portugal. ⁴Centro Cardiovascular da Universidade de Lisboa, Lisboa, Portugal. ⁵Scientific Advisory Board – Associação Portuguesa de Osteogénese Imperfeita, Lisboa, Portugal. ⁶IFIC Advisory Board – Associação Portuguesa de Osteogénese Imperfeita, Lisboa, Portugal

ABSTRACT

BACKGROUND: HRQoL is an important measure to evaluate the impact of a disease and the effects of medical intervention. Information on HRQoL may help health professionals to understand patients' comorbidities and to promote patient-centred care. Coping refers to the individual way of handling the external or internal stressors. There is evidence of an association between individual coping process and HRQoL in patients with chronic illness.

OBJECTIVES: This study aimed to measure HRQoL and Coping Strategies in a sample of Portuguese adults with OI.

METHODS: The WHOQOL questionnaire and the Brief Cope (Carver 1997) were used. Statistical analyses were performed using the statistical software package IBM SPSS Statistics, version 27. A total of 44 adults participated with a mean age of 39.91 (SD = 15.61), 74.4% were women, 71.4% had mild severity OI, and 84.1% had the COL1A1/COL1A2 gene mutation.

RESULTS: In general, participants showed good HRQoL. Worse results were found in the environmental domain. Problem focused coping strategies to face stressors were reported as more prevalent than emotional or avoidance strategies. Participants with the COL1A gene mutation reported more avoidance strategies compared with OI patients with other gene mutations. Physical domain and environmental domain of HRQoL were inversely correlated with age; women showed better results in the physical HRQoL domain than men. Avoidance coping was inversely correlated with disease severity and with HRQoL physical, psychological and social domains. All domains of HRQoL correlated with each other, with the association between physical and psychological domains, between psychological and environmental domain, and between social and environmental domain showing strong correlation values.

CONCLUSIONS: These results can contribute to a better understanding of the relationship between quality of life and the coping process and to improve the support of patients with OI considering their age. Results are discussed taking into account intrinsic (e.g., biomedical features) and extrinsic (e.g., cultural) variables of OI in this population.

P82

Technique of telescopic nailing of the femur by retrograde approach (FRA) in patients with osteogenesis imperfecta: clinical and radiological results

Zagorka Pejin¹, Lucas Chateaux¹, Mathilde GAUME², Ines MOSER¹, Marine De Tienda¹, Genevieve Baujat¹, Tristan Langlais¹, Georges Finidori¹, Stephanie Pannier¹

¹Necker Hospital, Paris, France. ²Necker hospital, Paris, France

ABSTRACT

OBJECTIVES: Telescopic nailing of the femur by antero-approach is the most common technique for the treatment of deformities and fractures in patients with osteogenesis imperfecta (OI). However, correction of deformities is uncertain with this approach, with a risk of residual coxa vara and inaccurate centering at the distal end of the femur. The objective of this work was to evaluate the clinical and radiological results of telescopic nailing of the femur by retrograde approach (FRA)

METHODS: This single-center retrospective study involved 23 children with a mean age of 3.5 years (min age 1-year, max age 12years), operated according to the FRA technique, between 2004 and 2019, unilaterally (7) or bilaterally (16), i.e. 39 FRA. Radiographs were used to evaluate the mean postoperative cervico-diaphyseal angle; the horizontality of the joint interline in frontal and sagittal plane, and the quality of the centering of the nail within the distal femoral epiphysis in frontal and sagittal planes. Joint mobility at one year follow-up, mechanical and infectious complications were recorded.

RESULTS: Mean follow-up was 2.3 years. Mean postoperative cervico-diaphyseal angle was $142^{\circ} \pm 10$. 92% of the patients had a postoperative cervico-diaphyseal angle greater than 130° . The horizontality of the postoperative joint interline in the frontal and sagittal planes was normalized in 90% of cases. The nail was centered in the frontal and sagittal planes in 87% (34/39). No complications related to the technique were reported. Knee mobility was unchanged at one year follow-up.

CONCLUSIONS: Telescopic nailing of the femur by retrograde approach allows a satisfying femoral axis correction, particularly the valgisation of the femoral neck, which is essential to reduce varus stresses, a source of recurrence of deformities and fractures. The alignment of the knee in the frontal and sagittal planes was corrected. In addition, the distal epiphyseal implant was centered, thus preserving the nail anchorage and telescoping effect.

P83

Ability of Radiofrequency Echographic Multispectrometry in the assessment of bone mineral density in subjects with Osteogenesis Imperfecta

Antonella Al refaie, Michela De Vita, Giulio Manzana, Elisa Giglio, Stefano Gonnelli, Carla Caffarelli

University of Siena, Siena, Italy

ABSTRACT

OBJECTIVE: Reduced bone mineral density (BMD) and increase risk of fragility fracture are common complication in subjects with Osteogenesis Imperfecta (OI). BMD by Dual-energy X-ray Absorptiometry (DXA) present several limits in subjects with AN. This study aimed to evaluate the usefulness of the new Radiofrequency Echographic Multi Spectrometry (REMS) technique in the assessment of bone status in subjects with OI.

METHODS: In a cohort of 22 subjects (36.9 ± 18.6 yrs) subjects with OI and in 24 healthy controls we measured BMD at the lumbar spine (LS-BMD), at femoral neck (FN-BMD) and total hip (TH-BMD) using a dual-energy X-ray absorptiometry device; moreover, REMS scans were also carried out at the same axial sites. Serum calcium, phosphate, creatinine, parathyroid hormone, 25-hydroxy-vitamin D, total alkaline phosphatase, bone alkaline phosphatase and C-terminal telopeptide of type 1 collagen were measured. Moreover, in OI subjects the presence

of prior fractures (hip, vertebrae, radius, humerus, tibia, perone) was reported.

RESULTS: A total of 86.4% of patients presented with a fracture history. The most common fracture sites were extremity long bones (femur, tibia-fibula and radius-ulna accounted for 18.2%, 54.5% and 27.3%, respectively) and at vertebral site (54.5%). BMD evaluated by DXA and REMS technique at all measurement sites were all significantly ($p < 0.05$) lower in subjects suffering from OI than in controls. Good correlations were detected between BMD by DXA and BMD by REMS measurements at TH ($p < 0.01$) in subjects suffering from OI.

CONCLUSION: This preliminary study has shown that REMS appears to be an accurate non-ionizing technology able to assess the bone status in subjects with OI. The attractiveness of the use of REMS for bone measurements in OI patients lies in its lack of ionizing radiation, its ease of use and the portability. In fact, the REMS device can be used directly on the patient's bed, and this could represent an excellent method for assessing the bone status even in OI subjects with a recent fracture. 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.

P84

The Severe Mouse Model of Osteogenesis Imperfecta Exhibits Compromised Cardiac Function

Brittany Lafaver¹, Li Lee^{1,2}, Krish Sardesai³, Julian Vallejo³, Evan Pierce³, Michael Wacker³, Lixin Ma^{1,2}, Maike Krenz^{1,4}, Charlotte L. Phillips¹

¹University of Missouri, Columbia, USA. ²Truman VA Hospital, Columbia, USA.

³University of Missouri- Kansas City, Kansas City, USA. ⁴Dalton Cardiovascular Research Center, Columbia, USA

ABSTRACT

Osteogenesis Imperfecta (OI) is a heritable connective tissue disease that affects 1:10,000 births. OI patients often present with brittle bones and scoliosis. Recent investigations have begun to elucidate the presence of inherent muscle weakness and cardiopulmonary complications. Previously cardiopulmonary complications were attributed to thoracic spinal deformities, however recent evidence demonstrates that patients with low grade or no scoliosis also exhibit cardiopulmonary manifestations. Echocardiographic clinical studies suggest that diastolic dysfunction in the OI patient population is common, often accompanied by valvular regurgitation. Of the extracellular matrix in the normal heart myocardium, approximately 85% of total myocardial collagen is type I, which is important in maintaining the structural integrity of the myocardium. Whether the presence of reduced or abnormal collagen levels alters cardiovascular health in OI patients remains to be fully elucidated, as cardiovascular complications are thought to be the second leading cause of death in OI. The osteogenesis imperfecta murine (*oim*) mouse models severe type III human OI in its homozygous (*oim/oim*) form. In the present study 4-month-old wildtype (Wt) and *oim/oim* littermates underwent functional studies, followed by sacrifice, where the hearts were weighed and flash frozen. Analyses of the wet weights of male and female *oim/oim* and Wt hearts demonstrated increased cardiac mass in *oim/oim* compared to age and sex matched Wt hearts. Preliminary cardiac MRI analyses demonstrated that *oim/oim* hearts exhibited increased left ventricular volume (end-diastole and end-systole) and decreased ejection fraction relative to Wt hearts. Initial electrocardiography studies suggest the conduction pathway in *oim/oim* hearts is not altered. Cardiac tissue evaluated by RT-qPCR showed elevated Brain Natriuretic Peptide (BNP) expression in the female *oim/oim* heart, as well as a myosin heavy chain (MHC) isoform switch, represented by lowered α -MHC and raised β -MHC in males. Overall these investigations suggest *oim/oim* mice demonstrate altered cardiac function as well as gene expression of BNP, indicating potential cardiac stress. Further investigations are needed to elucidate the mechanisms in the pathogenesis of the cardiac manifestations in the *oim/oim* heart and its implications to cardiovascular health in patients with OI.

P85

Gene expression signatures in bone and heart tissue of a Col1a1^{+/Mov13} mice identify it as a challenging animal model for mild Osteogenesis Imperfecta

Lidiiia Zhytnik^{1,2}, Lauria Claeys¹, Lisanne E. Wisse¹, E. Marelise W. Eekhoff¹, Alessandra Maugeri¹, Gerard Pals¹, Nathalie Bravenboer¹, Dimitra Micha¹

¹Amsterdam UMC, Amsterdam, Netherlands. ²The University of Tartu, Tartu, Estonia

ABSTRACT

OBJECTIVES: Col1a1^{+/Mov13} (Mov13) is one of the scarce mouse models for mild Osteogenesis Imperfecta (OI) type 1. Mice were created with heterozygous retroviral insertion in the first intron of *Col1a1*, causing *Col1a1* haploinsufficiency common in OI type 1 patients. We aimed to characterize gene expression pattern of collagens and tissue-specific markers in bone and heart of Mov13 mice to evaluate the application of this model in preclinical studies of haploinsufficient OI.

METHODS: Bone and heart from 10 Mov13 and 10 wild type (WT) C57BL/6J mice (12 weeks of age) were investigated. Each group consisted of five females and five males. Bone RNA was isolated from right tibiae and femur with TRIzol. Heart RNA was isolated from the ventricles using the RNeasy kit. cDNA was synthesized (SuperScript VILO kit) and qPCR was performed with SYBR Green mix. Both an unpaired T-test and a two-way ANOVA were performed as statistical analysis.

RESULTS: Bone tissue of Mov13 mice showed significantly higher expression of collagens (*Col1a2*, *Col5a1*, *Col5a2*), and bone metabolism markers (*Bglap*, *Fgf23*, *Smad7*, *Edn1* and *Elastin*) compared to WT. In gender subgroups, these differences were only significant for males. In contrast to our expectations, no significant differences in *Col1a1* bone expression were present, also in female and male subgroups separately.

Hearts of Mov13 mice showed higher expression of collagens (*Col1a1*, *Col1a2*, *Col3a1*, *Col5a1*, *Col5a2*), cardiological markers (*Tbx20*, *Ost*), immune markers (*Tnfa*, *Il10*), and lower expression of Regr compared to WT. In gender subgroups only male Mov13 showed significant differential expression in a number of genes (*Col1a2*, *Col3a1*, *Col5a1*, *Col5a2*, *Il10*, *Tbx20*, *Regr*).

CONCLUSIONS: Although reduced expression of *Col1a1* was observed in heart tissue, it was not present in bone, highlighting the possible alteration of tissue-specific expression of *Col1a1* in Mov13 mice, due to retroviral insertion in intron 1 of *Col1a1*. As *COL1A1* haploinsufficiency in bone is the main defect in OI type 1, Mov13 mice offer a limited representation of the disorder. Considering numerous reported leukemia cases and the challenging variability of Mov13 bone phenotype, a new reliable mouse model which recapitulates mild OI, is urgently needed to facilitate mild OI research.

FUNDING: Horstingstuit Foundation and the Estonian Research Council (PUTJD1009).

P86

Vertebral fractures in Osteogenesis imperfecta with COL1A1 and COL1A2-mutations

Bianca Link, Timothée Ndarugendamwo, Cecilia Giunta, Marianne Rohrbach

University Children's Hospital Zurich and University of Zurich, Zurich, Switzerland

ABSTRACT

BACKGROUND: Osteogenesis imperfecta (OI) is characterized by bone fragility resulting in fractures of long bone and vertebral bodies as well as skeletal deformities. Soft tissue change aggravate the bone features and generate a multisystemic disease including eye, ear and heard involvement.

PRESENTING PROBLEM: Treatment approaches in OI have to be multidisciplinary, with bisphosphonates (BP) as the primary

pharmacological intervention. Evidence is given for reduction of fracture risk and improvement in vertebral size and shape in children with BP therapy.

Although genetics provides insights into the molecular pathogenesis it is complex. The reason why increased bone brittleness is associated with other changes remains still unclear. Therefor predicting the risk for vertebral fractures (VF) is challenging.

CLINICAL MANAGEMENT: Of a cohort of 66 COL1A1/COL1A2 OI patients, we present 9 patients with VF (6 COL1A1 and 3 COL1A2 patients). All 9 patients presented with blue sclera and hypermobility. No hearing impairment was documented. Age at first fracture of long bones varied from prenatal to 10 y, age at first VF from 0.25 to 30 y. VF occurred mainly in the thoracic and lumbar spine. In one patient additional cervical spine fracture had been documented. Associated spine deformities were reported in 5 patients and spondylolisthesis in 2 patients. 5 patients received BP. 6 patients (4 COL1A1- and 2 COL1A2-patients) had dentinogenesis imperfecta.

DISCUSSION: The genotype/ phenotype correlation in autosomal dominant OI is complex with a clinical and intrafamilial heterogeneity. In this study, clinical manifestations and genetic variants in Swiss OI patients with VF were analyzed to expand the knowledge of the spectrum of disease.

Previous studies associated blue sclera with mild OI, while dentinogenesis imperfecta was frequently detected in moderate-to-severe patients. However, all patients with VF did show blue sclera and the majority dentinogenesis imperfecta as well as fractures of the long bones. 3 patients did show a severe course with a series of fractures from birth whereas 2 patients had the first fractures in adolescence. Thus VF have to be considered in any form of OI and may lead to diagnosis of OI being the first fracture in the course of the disease.

P87

Patient osteoblast model for Osteogenesis Imperfecta using induced mesenchymal stem cells

Lauria Claeys¹, Lidiiia Zhytnik^{1,2}, Vivi Heine^{3,4}, Ecem Yüksel¹, Elisabeth M.W. Eekhoff⁵, Nathalie Bravenboer⁶, Gerard Pals¹, Dimitra Micha¹

¹Amsterdam UMC, Department of Human Genetics, Amsterdam, Netherlands.

²University of Tartu, Department of Traumatology and Orthopaedics, Tartu, Estonia. ³Amsterdam UMC, Department of Child and Adolescent Psychiatry, Amsterdam, Netherlands. ⁴Amsterdam UMC, Department of Complex Trait Genetics, Amsterdam, Netherlands. ⁵Amsterdam UMC, Department of Internal Medicine Section Endocrinology, Amsterdam, Netherlands. ⁶Amsterdam UMC, Department of Clinical Chemistry, Amsterdam, Netherlands

ABSTRACT

OBJECTIVES: Osteoblasts are the collagen-producing cells in the bone tissue and play an important role in the pathophysiology of bone fragility in Osteogenesis Imperfecta (OI). However, osteoblast recruitment from patients needs an invasive procedure. iPSCs could be a source for the generation of an OI osteoblast model. The aim of the study is to generate osteoblasts from human dermal fibroblasts via an induced mesenchymal stem cell (iMSC) stage. Unlike primary MSCs, iMSCs maintain increased proliferation capacity and differentiation ability to osteoblasts, adipocytes and chondrocytes. Osteoblast generation from human dermal fibroblasts, could provide an OI-relevant cell model for studies of collagen regulation, osteoblast differentiation and therapy development.

METHODS: Fibroblasts of two healthy controls and two patients with glycine substitution mutations in COL1A1 (c.1678G>A (G560S) and c.2299G>A (G767S)) were reprogrammed to iPSCs. The iPSCs were subsequently differentiated to iMSCs via a neural crest cell stage (iNCCs). iMSCs were validated by trilineage differentiation to osteoblasts, chondrocytes and adipocytes. Cell-specific and ER stress marker expression of iPSCs, iNCCs, iMSCs and osteoblasts was tested by qPCR.

RESULTS: Control and patient fibroblast-derived iPSCs could be differentiated to iNCCs as shown by increased iNCC-specific markers *P75*, *AP2a* and *HNK1* and decreased iPSC marker OCT3/4 expression.

Similarly, iNCCs could be differentiated to iMSCs as shown by positive iMSC markers for *CD73*, *CD105* and *CD90* and negative iNCC and haemopoietic stem cell markers. The iMSCs could be differentiated to osteoblasts based on cell-specific marker expression and stainings (Alizarin Red and ALP). Increased expression of ER stress markers *DDIT3*, *SERPINH1*, *XBPI*+s and *HSPA5*, *DDIT3*, *SERPINH1*, *XBPI*, *XBPI*+s, *PDIA3* were noted only in patient osteoblasts and iMSCs respectively; *PDIA3*, *SERPINH1* and *XBPI*+s were significantly upregulated exclusively in patient iMSCs. No differences in ER stress marker expression were observed in iPSCs and iNCCs.

CONCLUSIONS: We have developed a procedure to differentiate human fibroblasts from both healthy controls and OI patients to iMSCs, and subsequently to osteoblasts. Patient iMSCs showed increased ER marker expression in line with the mechanism of OI in certain *COL1A1* glycine substitution mutations. This may potentially serve as a patient-specific cell model for the investigation of OI bone fragility and its pathological mechanism.

P88

Unfractured Care: Transforming Treatment Goals for the Infant with Severe Osteogenesis Imperfecta

Cristina McGreal, Jeanne Franzone, Richard Kruse, Michael Bober, Ricki Carroll

Nemours Children's Health, Wilmington, USA

ABSTRACT

BACKGROUND: Osteogenesis imperfecta (OI) is a rare condition that encompasses a wide phenotypic spectrum. However, the type of OI cannot be determined in utero.

PRESENTING PROBLEM: Many infants with a diagnosis of OI are classified as having type II or “lethal” OI before they are born. With this diagnosis, families are typically counseled on the options of termination and comfort care without being made aware of possible treatment options. However, improvements in prenatal and perinatal care have allowed us to implement strategies to increase the chance of survival.

CLINICAL MANAGEMENT: For families who opt for life-sustaining treatment, our center offers a trial of interventions, irrespective of the genotype or perceived phenotype in utero. Our multidisciplinary team consists of Maternal Fetal Medicine, Genetics, Orthopaedics, Palliative Care, and Neonatology. Our initial meeting begins prenatally and offers education around the diagnosis of OI, reviews the infant's images with the family, and discusses possible interventions and likely outcomes. Shared decision making with the family allows setting goals, managing expectations, and developing a total care plan prior to delivery.

Immediate access of critical care addresses respiratory support, nutrition, and pain management, with the institution of bisphosphonate therapy as soon as practical. Early education with the family allows safer transition to handling of the neonate, fracture care, and feeding, thus facilitating parental bonding and involvement in care.

DISCUSSION: The improved outcomes of what was previously considered “lethal” OI has changed our care paradigm. Our team-based approach to care for these complex infants, prenatally and perinatally, has improved survivability. For families who choose medical interventions, we offer an individualized plan of care and do not allow the “lethal” diagnosis to dictate management. Eight infants prenatally diagnosed with “lethal” OI were cared for by our multidisciplinary team starting in utero, and all are alive and thriving today. Elaboration of patient specifics and care will further highlight this care paradigm.

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Cardiovascular involvement in Osteogenesis Imperfecta - a Portuguese nation-wide cohort study (OI&Heart Study)

M Céu Barreiros^{1,2}, Andreia Magalhães^{1,2}, Mónica Rebelo¹, André Travessa¹, Patrícia Almeida Dias¹, Afonso Nunes Ferreira^{1,2}, M. Isabel Pinho¹, Susana Gonçalves¹, Laura Santos¹, Ana Paixão¹, Ana Almeida^{1,2}, Fausto Pinto^{1,2,3,4}

¹Centro Hospitalar Universitário de Lisboa Norte – Hospital Santa Maria, Lisbon, Portugal. ²Centro Cardiovascular da Universidade de Lisboa, Lisbon, Portugal. ³President, World Heart Federation, Geneva, Switzerland. ⁴Past President, European Society of Cardiology, Brussels, Belgium

ABSTRACT

Collagen mutations are the most common pathogenesis in Osteogenesis imperfecta (OI) and may affect extra-skeletal tissue. Although collagen type 1 has an important presence in cardiovascular system (CV), the impact of CV disease in OI is still unknown.

OBJECTIVES: Identify the presence of CV risk factors and cardiac disorders in OI pts

METHODS: Prospective study of 86 OI patients (pts) divided in two groups: Children (0-18 years) and Adults (>18 years), that were submitted to an evaluation protocol including: clinical assessment, ECG, transthoracic echocardiogram, 24hECG monitoring and 24h Ambulatory Blood Pressure Monitoring (ABPM). Adults repeated one year later.

RESULTS: Twenty children (45% male, 4-17 years; mild 85%, moderate 5% and severe 10% OI and gene mutation in COL1 89%) were included. 15% had excessive weight/ obesity as CV risk factor. No cardiac pathologies were identified.

Adult group included 66 pts (68% female, mean age 42 years (SD=16,11) with mild 75.4%, moderate 13.8% and severe 10.8% OI and gene mutation in COL1 87%). The most frequent reported symptom was palpitations (22%). CV risk factors were present in 24.8% of pts (obesity 42%, hypertension 34% and family history of CV disease 34%). ABPM detected hypertension in 37.5% pts. 14.3% of Holter monitoring showed minor findings and 2.6% showed moderate to severe findings (ventricular runs and tachycardia).

Echocardiogram identified left atrial enlargement (36%) and aortic dilatation (23%). Mitral regurgitation was detected in 28% of pts. A reduced Global Longitudinal Strain was found in 36% of pts and 6% had reduced left ventricular ejection fraction (LVEF). No significant differences were found in the evaluation carried out after one year.

Extra visits were performed in 5 pts mainly to introduce antihypertensive therapy and to investigate pts with reduced LVEF. 1 patient implanted a CRTD after hospital admission for malignant arrhythmic storm and heart failure.

CONCLUSION: OI pts seem to have CV system involvement, especially aortic dilatation and mitral valve abnormalities and these were evident only in the adult population. This prospective study, designed to address the global impact of OI in the CV system, intends to assess the evolution of these changes in a longer follow-up.

P90

Prevalence of tinnitus in adults with osteogenesis imperfecta

Sabrina Gonçalves¹, Adriana Silveira², Adriane Teixeira¹, **Temis Felix**²

¹Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. ²Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

ABSTRACT

OBJECTIVE: To verify the prevalence of tinnitus in osteogenesis imperfecta (OI).

METHODS: A cross-sectional, observational and descriptive study was performed. Individuals at least 18 years old, of both sexes and diagnosed with OI, living in different regions of Brazil were invited to participate

in this study. The survey was conducted through an electronic questionnaire that addressed sociodemographic and clinical issues.

RESULTS: 137 individuals participated in the study, 103 (75.2%) were female, with a mean age of 33.9 ± 12.2 years. Individuals were from all five regions of Brazil: 74 (54.0%) from the South, 47 (34.3%) from the Southeast, 3 (2.2%) from the Midwest, 11 (8.0%) from the Northeast and 2 (1.5%) from the North. Of these, 82 (59.9%) reported having tinnitus, 33 (40.2%) rarely and 49 (59.8%) constantly. As for the location of tinnitus, 54 (65.8%) individuals reported perceiving it only in one ear, 19 (23.2%) in both ears and 9 (11.0%) in the head. Of the total number of individuals with tinnitus, 35 (42.7%) individuals reported hearing loss, either unilateral or bilateral.

CONCLUSION: Tinnitus is a frequent symptom in the adult population with OI being more prevalent than in the general population, whose studies showed a prevalence of approximately 15%. This symptom is of multifactorial origin, with hearing loss being one of these factors. As seen in this study, not every individual with tinnitus reported having hearing loss, which indicates the need for further investigation into the causes of tinnitus in this population and the impact in the quality of life.

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Landscape of Osteogenesis imperfecta in Brazil: data from the Brazilian Rare Disease Network

Temis Felix¹, Bibiana Oliveira², Filipe Bernardi³, Mariane Neiva³, Erlane Ribeiro⁴, Rosemerie Abreu⁵, Antonette El-Husny⁶, Victor Ferraz³, Juan Llerena Jr⁷, Angelina Acosta⁸, Domingos Alves³

¹Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. ²Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. ³Universidade de São Paulo, Ribeirão Preto, Brazil. ⁴Hospital Infantil Albert Sabin, Fortaleza, Brazil. ⁵Universidade Estadual de Londrina, Londrina, Brazil. ⁶Hospital Bettina Ferro, Belem, Brazil. ⁷Instituto Fernandes Figueira, Rio de Janeiro, Brazil. ⁸Universidade Federal da Bahia, Salvador, Brazil

ABSTRACT

OBJECTIVE: The aim of this study is to present clinical data on osteogenesis imperfecta (OI) from the Brazilian Rare Disease Network (BRDN).

METHODS: BRDN is a consortium of 40 centers from all five regions of Brazil. Only 5 centers were OI Reference Centers. In the first phase, a retrospective data collection of cases attended at the centers in 2018 and 2019 was performed using a RedCap standard form. The prospective phase collects data in 2022. Here we report on data of the retrospective phase.

RESULTS: Of 11,319 records at BRDN, 359 (3.17%) OI cases were registered: 172 (47.9%) from the Northeast, 118 (32.9%) from the Southeast, 35 (9.7%) from the South and 19 (5.3%) from the North. The mean age was 18.5 years and 185 were male. Diagnosis of OI was confirmed in 318 cases and suspected in 41. For rare disease coding, Orpha terminology was used in 179 cases, ICD-10 in 176 and OMIM in 4. The majority (67.7%) did not have OI classification reported. In 56 cases OI was classified as type I, in 33 cases type IV, in 23 cases type III, 3 cases Bruck syndrome and 2 cases type II and 2 cases type V. Clinical diagnosis of OI was performed in 274 (76.3%) of the cases and in 36 (10%) molecular diagnosis was provided. In 21 cases prenatal diagnosis was observed. The 5 HPO most recorded were: recurrent fractures (116), increased susceptibility to fractures (52), blue sclerae (45), pathologic fractures (23), fractures of long bone (14). In 138 cases (38.44%) positive family history was observed and in 19 (5.29%) consanguinity was reported. Information of specific treatment for OI was registered in 197 cases: 143 pamidronate, 42 alendronate, 8 zoledronate and 4 teriparatide.

CONCLUSION: This data shows that most of the centers have a difficulty in clinical classification of OI. However specific treatment is offered by the centers. A poor access to molecular diagnosis was observed as this is not covered by the Public Health System. This data can contribute to public health policy and improve care of OI in Brazil.

FUNDING: Ministry of Health, CNPq

P92

Using the Bayley Scales of Infant and Toddler Development to assess fine and gross motor skills in young children with severe Osteogenesis Imperfecta

Emilie Hupin, Alex Bultitude, Catherine DeVile
Great Ormond Street Hospital, London, United Kingdom

ABSTRACT

OBJECTIVES: Osteogenesis Imperfecta (OI) is a bone fragility disorder usually caused by a defect in the genes which produce type 1 collagen. Features of severe OI include multiple fractures, bony deformities, hypermobility and weakness. Infants with severe OI follow an individual developmental pathway, typically achieving milestones later than non-affected infants.

There are no established valid and reliable outcome measures to assess early development in OI. However, therapists routinely use standardised tools to assess factors which may contribute to an infant's development. The Bayley Scales of Infant and Toddler Development (Bayley-III) is occasionally used in OI centres. The Bayley-III is an individually administered instrument that assesses the developmental functioning (cognitive, language and motor) of infants and young children.

METHODS: Therapists from a highly specialised centre for paediatric OI used the motor subscales of the Bayley-III to assess the fine and gross motor development of 5 children with severe OI, at ages 9, 18 and 24 months.

One child could not be assessed at 18 and 24 months due to fractures.

RESULTS: At each age interval, children achieved fine motor scaled scores within, or just below, the average range, with a mean score of 9 (where average scores are between 8-12).

Gross motor scaled scores were consistently below average, with a mean score of 1.

CONCLUSION: It is recognised that children with severe OI present with delayed motor development.

The Bayley-III identified marked delay in gross motor function in 5 children with severe OI. Four children maintained the same score over time, despite improvements in their abilities. This questions whether the Bayley-III is useful in capturing gross motor improvement in this population. In addition, some modifications to the assessment were necessary to accommodate the children's severe presentation, potentially impacting on the Bayley-III's validity.

Interestingly, fine motor scores were mostly within an average range at all intervals, thus speculating gross motor delay in this population may not impact significantly on fine motor function.

More research is needed to establish developmental trends, further explore the suitability of the Bayley-III in OI, and whether a bespoke motor developmental assessment tool for severe OI should be considered.

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Hearing in Osteogenesis imperfecta: a phenotype/genotype analysis

Adriana Silveira¹, Liliane Souza¹, Annanda Holtz², Sabrina Gonçalves², Adriane Teixeira², **Temis Felix**¹

¹Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. ²Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

ABSTRACT

OBJECTIVES: To verify the prevalence of hearing disorders according to genetic analysis and age group.

METHODOLOGY: Individuals with OI with a minimum age of 5 years, were included. Threshold pure tone audiometry was performed in all cases and compared to molecular analysis. The study was approved by local IRB (3233018500005327).

RESULTS: The sample consisted of 71 cases (142 ears), 44 females and 27 males with a minimum age of 5 and a maximum of 66 years (median

18±15.15 years). Of these, 73% had type I, 6% type III, 16% type IV, 4% type V OI and 1% type VII OI. The sample was divided into three groups according to age: G1 consisted of 33 patients (5- 20 years); G2 for 13 patients (21- 40 years) and G3 for seven patients (41- 66 years). Molecular analysis was available in 63.38% and half of these auditory thresholds was normal. Quantitative defect mainly in COL1A1 gene was observed in 49.35% of the sample and hearing loss was present in 60.52% of the ears. Qualitative defect with a predominance in the COL1A2 gene was observed in 34.5% and normal auditory thresholds was found in 66.07% of the ears. There was an increment in the number of ears with hearing loss according to aging. In the quantitative defect, 65% of the ears were altered in G1, 71.43% in G2 and 100% in G3. In the qualitative defect, no cases were observed in G3, but the same pattern of alteration was observed with 30.95% in G1 and 42.86% in G2. The variant c.-14C>T in IFITM5 was found in 3 cases with type V OI, one case belonging to each age group, and all of them presented hearing alteration. The single case type VII OI belong to G1 and the auditory thresholds were normal.

CONCLUSIONS: The findings of this study demonstrate that advancing age established a higher percentage of hearing loss. The quantitative defect in collagen genes showed a greater correspondence with the hearing alterations, and these cases should have audiometry performed regularly.

FUNDING: Decit/SCTIE/MS-CNPq-FAPERGS/08/2020 (21/2551-0000124-0) and CNPq (#306861/2019-4).

P94

Defining Pathomechanisms and Unique and Common Molecular Signatures of MBTPS2 Osteogenesis Imperfecta

Pei Jin Lim, Severin Marfurt, Uschi Lindert, Giulio Marcionelli, Marianne Rohrbach, Cecilia Giunta
University Children's Hospital Zurich and University of Zurich, Zurich, Switzerland

ABSTRACT

OBJECTIVES: X-linked recessive OI is caused by missense mutations in MBTPS2. Missense mutations in MBTPS2 in proximity to those found in OI cause also the dermatological condition IFAP/ KFSD without skeletal abnormalities. MBTPS2 encodes the site-2 protease (S2P), which by regulated intramembrane proteolysis (RIP) activates transcription factors involved in bone (OASIS) and cartilage (BBF2H7) development, ER stress response (ATF6) and lipid homeostasis (SREBP). The pathomechanism underlying MBTPS2-OI has not been exhaustively investigated and remains yet to be understood. In order to shed light into the pathomechanism of MBTPS2-OI and identify unique as well as common molecular players involved in the regulation of bone homeostasis, we applied transcriptome profiling on skin fibroblasts.

METHODS: We investigated gene expression changes by RNA-sequencing of cultured fibroblasts obtained from MBTPS2-OI and IFAP/KFSD patients, COL1A1-OI patients and healthy donors. Furthermore, we applied immunofluorescent staining to investigate the extracellular matrix deposited in culture by skin fibroblasts. Lipids were measured by GC-MS/MS.

RESULTS: SREBP-dependent genes SCD, FADS1 and FADS2 which are involved in fatty acid metabolism are downregulated in MBTPS2-OI but not in COL1A1-OI. This is coupled with alterations in the relative abundance of fatty acids in MBTPS2-OI fibroblasts. Furthermore, we identified unique gene expression changes in OI cells for genes involved in bone and cartilage development that are unaltered in IFAP/KFSD cells. The OASIS-dependent gene CHST3 involved in skeletal development is downregulated in both MBTPS2-OI and in COL1A1-OI compared with controls. The genes VEGFA, ADAMTS12 and DKK1, which are involved in bone or cartilage homeostasis are differentially expressed in both MBTPS2-OI and COL1A1-OI fibroblasts.

CONCLUSIONS: Our study showed alterations in the expression of genes involved in lipid metabolism, coupled with changes in the relative ratios

of cellular fatty acids that may affect bone health. Changes in genes involved in cartilage and bone development were also observed, while immunofluorescence staining revealed a reduction in collagen deposition in the ECM. Our findings generate new insights into biological molecules and pathways that could be relevant to the disease progression of OI and open up new hypotheses on the pathomechanisms underlying OI to be tested using *in vitro* and *in vivo* models of skeletal development.

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Therapeutic Management of Olecranon Fractures in Paediatric Osteogenesis Imperfecta

Lisa Mills, Amy Brammar, Christine Burren
Bristol Royal Hospital for Children, Bristol, United Kingdom

ABSTRACT

BACKGROUND: Osteogenesis Imperfecta (OI) is a disorder of collagen characterised by bone fragility and ligament laxity. Olecranon fracture in the general paediatric population is considered atypical with an incidence of 4%. It is more common within paediatric OI^[1, 2]. The rate of contralateral olecranon fracture within OI is high^[2]. Incidence, risk factors, therapeutic management and functional outcomes following olecranon fractures within paediatric OI is not well described.

PRESENTING PROBLEM: Children sustaining olecranon fractures in the last 5 years were identified within a supra-regional OI Service. Mechanism of injury, medical management, therapy management and functional outcomes are described.

Seven males, median age 11 years, with type 1 OI, sustaining a total of ten fractures were identified, accounting for 7.6% of the paediatric OI cohort. All fractures were sustained following fall from standing height. Contralateral fractures occurred in 2/7. First fracture occurred in the non-dominant side with mixed severity. 3/10 fractures were compound. 8/10 required surgical management. 3/7 children received bisphosphonates, 4/7 were bisphosphonate naïve.

CLINICAL MANAGEMENT: All children received at least one review by OI Therapists. 4/7 children (7/10 fractures) required ongoing input; three by OI team, (including 3 compound fractures) and one by local services. Physiotherapy included range of movement (ROM) and strengthening exercises. Occupational Therapy, available from OI Team only, focused on functional skills and scar management. One child required Psychology.

At six months post injury, 5/7 children regained full ROM and near normal function. Persistent deficits included loss of elbow extension ≤15 degrees and difficulty with strength-based tasks.

DISCUSSION: Olecranon fractures are common in type 1 OI. No consensus on therapeutic management or preferred outcome measures exists in OI population. Functional outcome was influenced by severity of injury and access to appropriate therapies. We suggest including strengthening the contralateral side and counselling on the risk of contralateral fracture. Further collaborative research is required to improve consistency of therapy management.

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Audiological follow up in Osteogenesis Imperfecta

Adriana Silveira¹, Sabrina Gonçalves², Andressa Otavio², Adriane Teixeira², **Temis Felix¹**

¹Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil. ²Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

ABSTRACT

OBJECTIVE: To describe an audiological longitudinal follow-up in Osteogenesis Imperfecta (OI).

METHODS: This observational, longitudinal and analytical study was approved by local IRB (number 3233018500005327). All subjects were recruited from the OI Clinic at Hospital de Clínicas de Porto Alegre, Southern Brazil. Audiological evaluation was performed using pure tone audiometry (0.25 to 8KHz) in an acoustic cabin with AC40 Interacoustics® equipment using TDH 39 and DD45 headphones for airway and model B71 and B81 for bone conduction. Evaluations were performed at the time set “1” from 2015–2017 and “2” from 2019–2021.

RESULTS: 37 subjects were enrolled, being 56.8% female. All subjects were evaluated twice with a time interval of 3 years. The mean age was 19.59 years (SD: 13.84, minimum 5 and maximum 55 years); 23 years (SD: 13.75, minimum 8 and maximum 58 years) in time “1” and “2” respectively. Type I, III, IV and V OI were evaluated, with a predominance of type I OI (67.57%). 52.37% of the ears evaluated at time “1” were considered normal, decreasing to 43.32% at time “2”. The average obtained in the frequencies of 0.25, 0.5, 1, 2, 3, 4, 6 and 8KHz in the airborne assessment of the right ear was 13.91dB and 15.67dB in the left ear at time “1”. No difference was observed between the airway obtained at time “1” and “2” in the right ear. In the left ear, the difference was 0.27dB. As for the bone pathway, there was a greater difference reaching 0.75dB on the right and 0.57dB on the left. These data showed a slow and steady worsening of airway conduction, but a steady worsening of bone conduction over time.

CONCLUSION: The results showed a slow hearing impairment in this population mainly due to bone conduction, suggesting that audiometric monitoring is recommended for a better understanding of hearing loss in this population and early intervention.

FUNDING: Decit/SCTIE/MS-CNPq-FAPERGS/08/2020 (21/2551-0000124-0) and CNPq (#306861/2019-4).

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Traumatic and non-traumatic cervical spine pathology in Severe, Complex and Atypical Osteogenesis Imperfecta

Catherine DeVile¹, Jeremy Allgrove¹, Belinda Crowe¹, Alistair Calder¹, Christine Burren², Toby Candler², Suma Uday³, Vrinda Saraff³, Nicola Crabtree³, Amaka Offiah⁴, Paul Arundel⁴

¹Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom. ²University Hospitals Bristol & Weston NHS Foundation Trust, Bristol, United Kingdom. ³Birmingham Women's and Children's NHS Foundation Trust, Birmingham, United Kingdom. ⁴Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom

ABSTRACT

OBJECTIVES: In England, services for children aged 0–18 years with Severe, Complex and Atypical Osteogenesis Imperfecta (OI) are managed by 4 centres (Birmingham, Bristol, London, Sheffield) in a Highly Specialised Service (HSS). Data are collated with reportable outcomes to NHS England, including radiological imaging findings of spine (vertebral fractures and scoliosis) and skull base (basilar invagination).

Cervical spine pathology is recognised in OI but the literature on cervical spine fractures and other cervical spine pathology is limited, especially with the increasing spectrum of OI and new genotypes.

METHODS: To review the number of children across the HSS in 2021/2022 with documented traumatic and non-traumatic cervical spine pathology to inform prevalence, genotype, age at injury, mechanism and outcome. This study did not include patients with known basilar invagination or intracranial pathology.

RESULTS: Total number of children within the OI HSS for year 2021/2022 = 310 (approximately 1/3 of total cohort of patients managed across the 4 centres). Of these, 21 had cervical spine pathology, subdivided into traumatic (n=10, aged 9 weeks to 14 years) and non-traumatic (n=11, aged 0.5–14 years).

TRAUMATIC INJURIES: Significant trauma history mostly involving hyperextension of neck, n=6. Of these, only 3 patients had a type 1 collagen gene variant, the remainder with type 6 (*SERPINF1*) (n=1),

type 8 (*P3H1*) (n=4) and *KDELR2*-related OI (n=2). Radiological findings: C1/2 pars/fractures in the majority. Neurological outcome: Normal.

NON-TRAUMATIC PATHOLOGY: Found on incidental radiological screening. Most common abnormality was at C2/C3 with subluxation, kyphosis and/or abnormal primary anatomy. Five children had OI type 11 or Bruck syndrome (*FKBP10* or *PLOD2* gene variants); they had the most severe cervical spine pathology, associated with spinal canal narrowing and myelopathy (n=2), one of whom was tetraplegic.

CONCLUSION: Although uncommon, traumatic and non-traumatic cervical spine pathology was equally represented across the cohort with increased prevalence in children with non-collagenous gene variants. Traumatic injuries had a good neurological outcome.

Children with OI type 11 or a Bruck phenotype (*FKBP10* or *PLOD2* gene variants) appear predisposed to abnormal cervical spine anatomy and should receive early and ongoing screening with appropriate radiological cervical spine imaging.

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Proteomic analysis of the vertebral column in dominant OI zebrafish models to reveal biomarkers for phenotypic outcome

Andy Willaert, Sophie Debaenst, Hanna De Saffel, Paul Coucke
Center for Medical Genetics, Department of Biomolecular Medicine, Ghent University, Ghent, Belgium

ABSTRACT

OBJECTIVES: Osteogenesis imperfecta (OI) is mainly caused by dominant mutations in either the *COL1A1* or *COL1A2* genes, encoding type I collagen. Different mutations in these genes can lead to a different clinical outcome, while the molecular mechanisms underlying this phenotypic variability are largely unknown. The identification of a molecular signature ('biomarkers') for these different outcomes is therefore highly desirable. Such biomarkers not only have diagnostic value, but will allow stratification by OI type, have predictive value towards progression of the clinical presentation and will play a role in treatment guidance.

METHODS: To identify potential biomarkers in dominant OI, we employed three OI zebrafish models, carrying different glycine substitutions in type I collagen (*coll1a1*^{dc124/+}, *coll1a2*^{mhl5/+}, *coll1a1*^{mhl13/+}), and showing variability in phenotypic severity. Protein was extracted from the vertebral column of each of these mutants (n=5) and matched controls (n=5), and subjected to mass spectrometry (MS)-based shotgun proteomics. Comparative analysis of differentially abundant proteins between mutants and their respective controls was done to reveal mutant-specific biomarkers.

RESULTS: In a first step, three different described protein extraction methods were tested on wild type zebrafish vertebral bone, either using SDSwDTT, Trizol or a guanidine-HCl (GdmCl) solution. The latter method resulted in very low numbers of peptides and identified protein groups because of issues with sample preparation, purification and solubility. When comparing SDSwDTT and Trizol extraction methods, similar results were obtained with identification of a total of 9946 peptides and 1826 protein groups of which 805 that could be reliably quantified. Analysis of differential protein abundance revealed that 148 and 92 proteins were respectively up- and downregulated in SDSwDTT versus Trizol samples. Nevertheless, both methods were capable of extracting the majority of the known bone-specific and matrix proteins from the vertebral column. We then used Trizol to extract protein from the above-described OI zebrafish models and matched controls and performed LC-MS/MS analysis. Data analysis is ongoing.

CONCLUSION: We optimized a protocol for protein extraction from the zebrafish vertebral column, followed by quantitative mass spectrometry analysis. In this way, the zebrafish is a promising model for the identification of biomarkers for phenotypic outcome in OI.

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Promoting Inclusion in Physical Education for Children with Osteogenesis Imperfecta: Preliminary Findings and Input Warranted for Guideline Creation

Galil Osman¹, Jessica Chemtov², Georgia Powell¹, Chantal Damas³, William Harvey², Louis-Nicolas Veilleux^{3,1}, Frank Rauch^{1,3}, Argerie Tsimicalis^{1,3}

¹McGill University, Faculty of Medicine and Health Sciences, Montreal, Canada. ²McGill University, Faculty of Education, Montreal, Canada. ³Shriners Hospitals for Children-Canada, Montreal, Canada

ABSTRACT

OBJECTIVES: The objectives of this in-progress study are: (1) to review the literature on the inclusion of youth with osteogenesis imperfecta (OI) in physical activity settings such as team sports, physical education classes, and extracurricular activities; (2) formulate guidelines, strategies, and recommendations for the inclusion of youth with OI in physical activity settings; and (3) create a concise, accessible, and user-friendly tool that assists in applying modifications to physical activities.

METHODS: Guided by the process of developing evidence-informed guidelines, an interprofessional task force composed of one nurse scientist, one physical therapist, one adapted physical activity specialist, one kinesiologist, one medical doctor, and three trainees was convened. Other experts, members are to be recruited. The process entails: (1) reviewing and synthesizing the literature derived from academic (Ovid, Medline, CINAHL, PSYCInfo) and grey literature sources, (2) developing guidelines, and (3) creating a clinically meaningful, person-focused tool to facilitate the inclusion of children and adolescents with OI into the physical activity settings.

RESULTS: To date, a paucity of empirical studies (e.g., case reports, clinical examples, and non-experimental studies), grey literature (e.g., OI organizations and government guidelines) have been retrieved. Input from clinical, teaching, and patient experiences are needed to help devise the tool to optimize physical activities such as: team sports, individual sports, and strength and conditioning.

CONCLUSION: These activities were prioritized due to the evidence and; however, input from other experts is needed. As this is an ongoing, interactive process, the task force is actively seeking feedback from conference attendees. As such, the study personnel would like to request time to be prioritized and allocated for discussion of these preliminary results, inform the drafting of the guidelines, and strategies and recommendations. Efforts to foster inclusivity in physical education settings will require ongoing, sustainable collaborations and partnerships between the students' healthcare providers and school systems.

P100

Osteogenesis Imperfecta Clinic Implementation of patient reported outcome measures (PROM): Implications, Pitfalls, Strategies, and Progress

Maureen Donohoe¹, Cristina McGreal¹, Kenneth Rogers¹, Richard Kruse¹, Jeanne Franzone²

¹Nemours Children's Health-Delaware, Wilmington, USA. ²Nemours Children's Health- Delaware, Wilmington, USA

ABSTRACT

BACKGROUND: Importance of PROM has been established with the OI population to assist in shared decision making and to understand treatment related issues. Initial PROM implementation with paper format allowed small sample size. Transition to electronic version enhanced the capture rate. Our learning opportunities provide insight for others interested in implementing electronic PROMIS. Survey goals: annual baseline information, understanding quality of life outcomes and supporting goals of patient.

PRESENTING PROBLEM: Only a small sample size was captured with clinician distributed paper surveys, hand scored and recorded into the medical record. Over 32 months, 58 individuals responded with 124 paper surveys, 40 were repeatable measures. In 33 months of electronic

use, 232 individuals completed with 1004 surveys, 116 had repeatable measures. 94 patients had patient portal accounts.

CLINICAL MANAGEMENT: PROMIS questionnaire is linked to the medical record number within the EPIC. Multiple clinicians/staff are responsible for collecting data, understanding scores, and reviewing scores with family. Clinicians see individual and group trend analysis based on demographic and clinical factors.

DISCUSSION: Implications: Seven months after implementation, COVID related restrictions significantly altered the PROM process. When restrictions eased within the hospital, electronic capture of PROMS increased. During this time, improvements were made to improve presentation of data within EPIC, increase education of staff, and implemented improvements to encourage families to complete using the patient portal to decrease time to complete in clinic.

Pitfalls: Past paper data is not easily comparable to electronic data. Child report (10-18 years) is more reliable while parent proxy (5-18 years) has better longevity. Adult data has similarities and differences, losing comparison with teen scores. Cancel/ reschedule appointments may lose surveys.

Strategies: Gather and educate a team. Have a superuser to support. Get family investment through education and ease of access. Put in hard stops to prevent lost data. Review data and remind of future surveys.

Progress: Increasing surveyed individuals with repeatable data allows real time findable and comparable data in the medical record. Useful for tracking individuals and populations compared to general population.

P101

Evaluation of Radiolucent Lesions in Cortices of Long Bones in Osteogenesis Imperfecta Patients

Carolyn Cook¹, Teresa Cappello², Peter Smith²

¹Chicago Medical School at Rosalind Franklin University, North Chicago, USA. ²Shriners Children's Hospital, Chicago, USA

ABSTRACT

Osteogenesis imperfecta (OI) is a bone disorder characterized by an abnormality in collagen. It is typically diagnosed before or after birth, and has a variety of clinical features. The defect in collagen production contributes to the radiographic appearance of this disorder, and is characterized by cortical bone thinning and increased transparency of the trabecular bone. Limb deformities are common, including leg length discrepancies and bowing. In some cases, patients may develop lytic bone lesions in the cortices of their tibiae or femora. The occurrence of these lesions in the long bones of children is unknown. In a retrospective study, lower extremity radiographs of 352 pediatric patients with OI seen at Shriners Hospital for Children in Chicago, IL between 1926 through February 2022 were examined to determine the incidence and clinical course of these lesions. The radiographs of these patients were reviewed in three separate modalities, including in the electronic medical record (EMR), scanned into the Shriners database, and hard copy images. Of the identified patients 180 (51.1%) were male and 172 (48.9%) were female. There were multiple OI subtypes represented in this cohort including 75/352 (21%) patients with Type I OI, 40/352 (11%) patients with Type III OI, 48/352 (14%) patients with Type IV OI, 3/352 (1%) patients with Type V OI, 1/352 (0.2%) patient with Type VIII OI, 7/352 (2%) patients classified as "other" subtypes, and 178/352 (51%) patients not classified by the Sillence criteria. Lesions were present in 104 (29.5%) of the 352 patients. A total of 208 of the positive radiographs were reviewed, and lesions were present on 121 (58.1%) tibiae and 79 (37.9%) femora. In 186 (89.4%) of the radiographs, the lesion was present on the diaphysis of the long bone. These findings warrant further evaluation into the long-term outcome of this radiographic abnormality.

P102

Design and Development of an E-Health Program for Youth with Osteogenesis Imperfecta – Teens OI

Raissa Passos dos Santos¹, Frank Rauch¹, Jennifer Stinson², Khadija Chougui³, Laura Massochin Nunes Pinto³, Louis-Nicolas Veilleux¹, Mitchell Bernstein¹, Noemi Dahan¹, Reggie Hamdy³, Sofia Addab³, Argerie Tsimicalis¹

¹McGill University, Montreal, Canada. ²Sick Kids Hospital, Toronto, Canada. ³Shriners Hospital, Montreal, Canada.

ABSTRACT

OBJECTIVE: There is an urgent need for innovative approaches to address the self-management needs of young adults with osteogenesis imperfecta (OI) transitioning into adult-oriented health care systems. A promising field, self-management interventions, delivered over the internet, can improve selected outcomes in certain childhood illnesses. The objective of this in-progress study is to design and develop a web-based program to support self-management and transitional care for youth with OI, parents and health care professionals.

METHODS: A user-centered, qualitative design was chosen, including creating a “Website Design and Development Council” and actively seeking input from youth/parent dyads and OI experts (via Symposia sessions). The design and development of the website is guided by Garrett’s Theory of User Experience, which includes 5 different planes of a website that affect the user experience: surface, skeleton, structure, scope and strategy, and will be descriptively analyzed accordingly.

Preliminary RESULTS: A 6-person interdisciplinary council has been convened to work collaboratively with the research team. The council consists of 4 healthcare professionals (2 nurses and 2 social worker) and 2 patients (1 youth, 1 parent). Ten semi-structured interviews have been completed by a young adult with OI with 7 youth and 4 parents. Youth ages varied from 14 to 20 years old, and OI types included types I, III, and IV. Three planes of the user experience have been explored to date, including the content for the preliminary Structure Plane element. Key website features to be included are: Getting started; What is OI; Pain; Psychological Issues; Social Issues; Treatment or Care for OI; Managing Symptoms; Looking ahead.

CONCLUSION: The present study focuses on youth as early adopters of e-health technologies, which can assist them in coping with their OI, support their health-related quality of life and facilitate a successful transition to adult health care. The study is open to recruitment for in-person interviews at Shriners Hospitals for Children®-Canada and remotely for local and global input. Therefore, we welcome opportunity to collect further data from OI experts and community at the conference.

P103

Skeletal Muscle Mitochondria Function in Osteogenesis Imperfecta Murine and G610C Mouse Models

Tara K Crawford¹, Victoria L Gremminger¹, Catherine L Omosule¹, Youngjae Jeong¹, Rory Cunningham¹, Grace M Meers¹, R. Scott Rector^{1,2}, Charlotte L Phillips¹

¹University of Missouri, Columbia, USA. ²Harry S. Truman Memorial Veterans’ Hospital (VA), Columbia, USA

ABSTRACT

Osteogenesis imperfecta (OI) is a rare heritable connective tissue disorder causing bone fragility, primarily due to type I collagen mutations. Other hallmarks include short stature, cardiopulmonary complications, dentinogenesis imperfecta, and skeletal muscle weakness. Roughly 80% of mild to moderate OI patients exhibit muscle weakness, and although muscle weakness is present in certain OI mouse models, the pathogenesis remains to be elucidated. Historically muscle weakness was attributed to reduced activity, but is now known to be intrinsic in the severe homozygous OI murine (*oim*) mouse model contributing to reduced contractile generating force. The *oim* skeletal muscle weakness is associated with mitochondrial dysfunction, and the

mild to moderate *+G610C* mouse has bone fragility in the absence of reduced contractile generating force and muscle weakness.

In the current study, we evaluate *oim* and *+G610C* OI skeletal muscle to investigate potential differences in their mitochondrial function. We investigated male wildtype (WT), *oim* and *+G610C* mitochondrial function through direct evaluation of mitochondrial respiration rates in isolated gastrocnemius mitochondria and evaluation of whole muscle gastrocnemius homogenates by western blot analyses for Electron Transport Chain (ETC) complexes and markers of mitochondrial biogenesis and mitophagy.

We observed that isolated gastrocnemius mitochondria from *oim* mice exhibited severe mitochondrial dysfunction as characterized by a 52% to 65% decrease in mitochondrial respiration rates, while *+G610C* mitochondrial respiration rates appeared less impacted. Though both models exhibited decreased state 3 respiration (electron flux through ETC complexes I and II). Interestingly, citrate synthase activity from whole muscle homogenate was decreased in *oim* yet increased in *+G610C* compared to WT littermates, suggesting potential compensation for altered mitochondrial respiration in the *+G610C* model. The levels of mitochondrial biogenesis markers PGC1- α and TFAM were increased in *oim* gastrocnemius, while equivalent in *+G610C*. Whereas mitophagy marker LC3II/I was decreased in *oim* and elevated in *+G610C* relative to WT, suggesting different mechanisms to combat or compensate for altered mitochondrial function.

These findings suggests that mild to moderate *+G610C* mice exhibit the ability to compensate for potential mitochondrial changes, potentially accounting for the absence of muscle weakness in the *+G610C* mouse that is present in the severe *oim* mouse model.

P104

Modification of the Osteogenesis Imperfecta Quality of Life Scale - Paediatric version (OIQoL-P) and Development of a Parent-Report version

Elizabeth Gibbons¹, Helen Doll², Christopher Hartford³, Katherine Durnell², Linda Abetz-Webb⁴, James Clancy⁵, Claire Hill⁶

¹Previously at Clinical Outcome Solutions, Folkstone, United Kingdom.

²Clinical Outcome Solutions, Folkstone, United Kingdom. ³Previously at Clinical Outcome Solutions, Folkstone, United Kingdom. ⁴Patient-Centred Assessments Ltd, Bollington, United Kingdom. ⁵Mereo BioPharma Ltd, London, United Kingdom. ⁶Sheffield Children’s Hospital, Sheffield, United Kingdom

ABSTRACT

OBJECTIVES: Evaluate the content validity of the 33-item OIQoL-P, modify and shorten as necessary, and develop a parent-report instrument (OIQoL-O) for younger children unable to self-report.

METHODS: Osteogenesis imperfecta (OI) is a rare genetic disorder of the connective tissue characterized by bone fragility and reduced bone mass. A literature review was conducted to explore the impact of OI on child health-related quality of life (HRQoL). Qualitative interviews were then undertaken in OI healthcare professionals (HCPs) in the United States (US n=2) and United Kingdom (UK n=2) to discuss the impact of the condition and assess the content validity of both the OIQoL-P and new OIQoL-O. Three rounds of interviews were conducted with a total of 15 parent and child dyads recruited from patient advocacy groups in the US and UK to inform sequential modifications of the measures. Each interview was conducted in two parts: concept elicitation (CE) to understand participants’ lived experience of OI and cognitive debriefing (CD) to examine the relevance, appropriateness, and understanding of OIQoL-P and OIQoL-O content (items, instructions, response options, recall period) in children and parents, respectively.

RESULTS: The OIQoL-P conceptual model was supported by the literature review. Both concepts present and not present in the model were discussed in the HCP interviews to inform revisions to the OIQoL-P. HCPs indicated potential redundancy in some items and suggested additional areas of clarification. The modified measures were found acceptable in the dyad interviews, with the items and instructions being well understood, although some items were considered to require a

longer recall period, and the relevance of others questioned. Issues were identified with the “never” response option in the context of a one-week recall period, and response distributions suggested some items of the OIQoL may not be perceived to be relevant by children with OI; their parents had a higher endorsement rate. The OIQoL-P was reduced to 26 items, with the same items mirrored in the OIQoL-O.

CONCLUSIONS: The revised and shortened OIQoL-P and OIQoL-O demonstrated acceptable content validity, and both are considered fit-for-purpose in assessing OI-associated HRQoL impacts in children. Quantitative evidence gathered in the intended context of use and psychometric analyses will inform further instrument properties.

P105

WHO-ICF Based Outcomes following Posterior Spinal Fusion with Instrumentation in a Child with OI Type III and Scoliosis- A Five-Year Follow-up

Frances Baratta-Ziska

Hospital for Special Surgery, New York City, USA

ABSTRACT

Spinal deformity is common in children with type III osteogenesis imperfecta (OI). Progressive spinal curves $>30^\circ$ are almost certain in children with OI type III. Thoracic scoliosis $>60^\circ$ in children with OI type III leads to adverse pulmonary function. Respiratory insufficiency is a leading cause of death in adults with severe OI.

For this child, posterior spinal fusion T2-L4 with instrumentation (PSF) and early physical therapy (PT) helped reduce these complications. Bone fragility in children with OI type III presents challenges for adequate spinal fixation, healing, early mobilization, and function.

The World Health Organization-International Classification of Function (WHO-ICF) model was used to organize findings. The Gross Motor Function Measure, Children's Assessment of Participation and Enjoyment, and the Gillette Functional Assessment Questionnaire Functional Walking Scale were used to compare function and participation pre-surgery, subacute post-surgery, and at 1 & 5 years post-surgery.

PRESENTING PROBLEM: To present the PT plan of care pre and post-surgery as there is little to no information in the literature about PT and rehabilitation for children with OI type III and scoliosis following PSF with instrumentation. This case report also aims to present the outcome measures used to assess body structure and function, activity, and participation levels for this child with progressive scoliosis and OI type III s/p PSF with instrumentation pre-op and post-op at 1 & 5 years.

CLINICAL MANAGEMENT: This case report aims to present the clinical decision-making rationale involved in the management of this child pre- and post-operatively.

DISCUSSION: Despite a diagnosis of OI type III, progressive scoliosis, bone fragility, and a complicated post-surgical course, early mobility and functional improvements were attained and maintained at 1 & 5 years post-op as assessed by outcome measures that are valid for children with disabilities including OI. This child with OI type III has resumed all pre-surgery activities pain-free and with greater ease of movement by 1-year post-op & maintained at 5-year post-op follow-up. Floor effects of outcome measures: Functional ability was improved but still below normative values, which may be due in part to those abilities that were too difficult or were not tested due to fracture risk receiving zero scores.

P106

Clinical and functional characterization of Osteogenesis Imperfecta Type XV: Single-centre Chinese Cohort

ZX Dong¹, PK Chen^{1,2}, ZJ Tan^{1,3}, HT Shek¹, YP Zhou¹, JC Xu¹, AM Qiu¹, LN Dong¹, Bo Gao^{1,2}, MKT To^{1,4}

¹Department of Orthopaedics and Traumatology, The University of Hong Kong-Shenzhen Hospital (HKU-SZH), Shenzhen, China. ²School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China. ³Department of Orthopaedics and Traumatology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China. ⁴Department of Orthopaedics and Traumatology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

ABSTRACT

INTRODUCTION: WNT1 (type XV) mutations represented the biggest group of autosomal recessive OI in China, and WNT1 signalling plays critical roles in bone healing and remodelling. However, long term results of the treatments were rarely reported in large cohort studies. Our single-center Chinese cohort may provide valuable information of this group of patients.

OBJECTIVES: This longitudinal research aims to understand the clinical characteristics of Type XV OI patients and to help develop treatment protocol.

METHOD: Prospective review of the type XV OI patients admitted to HKU Shenzhen Hospital between 2014 and 2022. The genetic mutation profiles were confirmed. Information including the onset of disease, number of surgeries, use of medication, X-rays, and BMD were reviewed. The mobility metrics included GFAQ and FMS were used to evaluate the patients' functional status. All information was retrieved from electronic medical record in the hospital.

RESULTS: A total of 24(10 males,14 females) Type XV OI patients were reviewed. Seven novel mutations of WNT1 were detected and 7 patients had homozygous WNT1 mutations. They all suffered from moderate to severe types of OI. The mean Z score of BMD before and after treatment were -5.2 and -3.2 respectively. Scoliosis and coxa vara were observed in 12 patients (50.0%) despite of age, with two underwent spinal surgeries. Seven (29.1%) of them had unilateral ptosis. 20% of the patients required walking aids. The deformities not only of lower limbs but also upper limbs were observed in 12 patients. Fourteen(63.6%)patients were performed bilateral lower limbs rodding surgeries. Patients needed revised surgeries 40% due to implants migration. Patients with homozygous mutations had worse GFAQ and FMS scores($p<0.05$). Younger patients under aggressive surgery plus bisphosphonate treatment could have higher GFAQ (3.6v.s.2.1)and FMS scores(3.6v.s.2.1).

CONCLUSIONS: Type XV OI differs from the classical OI, seems with relatively more revised surgeries. But better mobility outcomes can be achieved by offering standard treatments . More attention is needed for such patients in clinical practice. Early interventions are recommended for Type XV.

P107

A retrospective review of 496 orthopedic surgeries in 223 Chinese patients of osteogenesis imperfecta

Peikai Chen, Jingwei Wu, Yunzhi Lin, Jichun Xu, Zhijia Tan, Shijie Yin, Michael Kai Tsun To

The University of Hong Kong-Shenzhen Hospital, Shenzhen, Guangdong ⁵¹⁸⁰⁵³, China

ABSTRACT

OBJECTIVES: We retrospectively summarized all orthopedic surgeries performed on osteogenesis imperfecta (OI) patients in our hospital from 2013 to 2021.

METHODS: Medical records of all surgeries were retrieved. Physicians reviewed and classified the surgeries into osteotomy or non-osteotomy, planned or unplanned, plated or non-plated, etc. Unplanned surgeries

were defined as nail or plate breakage, infection, non-union or delayed union, re-fracture or casting adjustment. Planned surgeries included new fractures and new osteotomies. RUST scores were used for rating healing.

RESULTS: In all, 496 surgeries in 223 OI patients (95 female, 128 male) were performed from late 2013 to August of 2021. The patients' ages ranged from 0.5 to 38 years (interquartile-range [IQR], 5.7 to 14.4; average 11.4). Between 1 and 9 (IQR, 1 to 3; average 2.2) surgeries were performed per patient. Osteotomies were involved in 341 surgeries (68.8%), while non-osteotomies were involved in 155 surgeries (31.2%). The non-osteotomies involved one or multiple of these: casting adjustment or fixation (n=56), revision (n=48), fracture (n=38), removal of internal fixation (n=22), debridement (n=9), cranial traction (n=4) and spine surgeries (n=4). Among the osteotomies, 178, 135, 23 and 5 surgeries involved one, two, three and four bone segments, respectively. The most common sites are femur and tibia, being involved in 241 and 148 surgeries respectively. Only 27 surgeries were performed on the upper limbs. Seventy-five of the osteotomies (22.0%) were followed by some unplanned surgeries (n=118; average 1.6 times), which took place between 0 and 2066 days (IQR, 97 to 1053) after the first osteotomy. Locking plates were used in 48 osteotomies (36 patients) with an average age of 18.1 (IQR 13.8 to 21.6). By randomly choosing a group of age-matched unplated surgeries as controls, we found no difference in unplanned event rates between plated and unplated surgeries (χ^2 p=0.94).

CONCLUSION: A large number of orthopedic surgeries were reviewed. Locking plates were used in older patients, and their use did not seem to incur additional events or unplanned surgeries. Associations with genotypes and Sillence types warrant further investigations.

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P108

Clinical features and molecular characterization of Chinese patients with type XI osteogenesis imperfecta

Zhijia Tan^{1,2}, Hiu Tung Shek¹, Peikai Chen^{1,2}, Zhongxin Dong¹, Yapeng Zhou¹, Shijie Yin¹, Anmei Qiu¹, Lina Dong¹, Bo Gao^{1,2}, Michael To^{1,2}

¹The University of Hong Kong-Shenzhen Hospital, Shenzhen, China. ²The University of Hong Kong, Hong Kong, China

ABSTRACT

OBJECTIVES: To characterize the clinical and molecular outcome of FKBP10 mutations in type XI osteogenesis imperfecta

METHODS: Patients diagnosed with OI were recruited for genetic test. Sanger sequencing was applied to detect the splicing defect in FKBP10 mRNA. Bone structure was characterized by Goldner's trichrome staining. Bioinformatic analyses of bulk RNA sequencing data were performed to examine the effect of FKBP10 mutation on gene expression.

RESULTS: Here we report 6 type XI OI patients with FKBP10 mutations from 4 different families. All patients showed spinal deformity and the three children from a consanguineous family developed early onset scoliosis. The homozygous mutation identified in the fifth intron of FKBP10 (c.918-3C>G) in this family led to abnormal RNA processing and loss of FKBP65 protein, and consequently resulted in aberrant collagen alignment and porous bone morphology. Analysis of transcriptomic data indicated that genes involved in protein processing and osteoblast differentiation were significantly affected in the patient derived osteoblasts.

CONCLUSION: Our study characterized the clinical features of OI patients with FKBP10 mutations and revealed the pathogenesis of the c.918-3C>G variant. The histological and transcriptomic analyses helped to gain insight into the roles of FKBP10 mutations on collagen processing and osteoblast differentiation.

LM1

Self-perception on quality of life of children and adolescents with Osteogenesis Imperfecta attended in a University Hospital

Leilah Alves¹, Lara Torreão¹, Amanda Reinert¹, Renata Lago²

¹UFBA, Salvador, Brazil. ²UFRB, Santo Antonio de Jesus, Brazil

ABSTRACT

OBJECTIVES: Osteogenesis Imperfecta (OI) is a chronic disease with no known cure that can affect the quality of life (QoL)^{1,2}. Most studies that evaluate children's QoL have parents or caregivers as informants³⁻⁹. However, proxy reports are not always convergent with self-reports, and children can reliably express opinions and feelings about their own QoL if age-appropriate instruments are used³⁻⁹. In this study, we aim to evaluate the QoL of pediatric patients with OI, based on their own health perception.

METHODS: The validated questionnaire Kidscreen-52, containing objective questions regarding ten domains of children and adolescent's quality of life¹⁰⁻¹², was applied to 31 patients aged 8 to 20 years that received routine treatment from June 2018 to December 2019. Data obtained was scored as Rasch scales and then translated into T-values based on parameters from the international survey sample from 12 European countries¹⁰.

RESULTS: Half of the patients were female (n=16, 51,52%), the mean age was 13,5 years, and the median age was 14 years. The results showed QoL scores on average for most domains addressed by Kidscreen-52. Only the dimension Health and Physical Activity had a low QoL outcome, and the dimension School Environment scored above average.

CONCLUSION: Children and adolescents with OI showed a satisfactory QoL in nine out of ten Kidscreen-52's domains, including Social Acceptance and Bullying, which was a dimension of special interest in this age group. Health and Physical Activity was the only exception; negative results were foreseen in this area due to the disease's impact on physical function^{2,13}. Some discrepancies were detected between answers within each QoL domain, requiring more specific future investigations. Furthermore, the School Environment domain exceeded expected levels. Although some studies report that people living with OI often present above-average QoL scores in emotional and psychosocial domains^{14,15}, no similar results were found in the literature for the school environment. Considering the social profile of the study sample, it is possible that school is seen by these patients as the place where they feel the safest. Subsequent studies with larger samples and associated qualitative analysis are warranted for a deeper comprehension of these findings.

LM2

Type I collagen homotrimer exacerbates the impairment of bone structural properties caused by the osteogenesis imperfecta murine mutant allele, despite not itself causing bone fragility

Katie Lee¹, Lisa Rambault², George Bou-Gharios¹, Peter Clegg¹, Riaz Akhtar¹, Gabriela Czanner³, Rob van 't Hof¹, Elizabeth Canty-Laird¹

¹University of Liverpool, Liverpool, United Kingdom. ²Université de Poitiers, Poitiers, France. ³Liverpool John Moores University, Liverpool, United Kingdom

ABSTRACT

OBJECTIVES: The aim of the study was to determine whether the abnormal homotrimeric form of type I collagen causes bone fragility given the osteogenesis imperfecta murine model produces solely the homotrimeric form. Type I collagen is the major structural component of bone where it normally exists as an $(\alpha 1)_2(\alpha 2)_1$ heterotrimer in all vertebrates. The osteogenesis imperfecta murine model comprises solely homotrimeric $(\alpha 1)_3$ type I collagen, due a dysfunctional $\alpha 2$ chain and has a brittle bone phenotype implying that the heterotrimeric form is required for physiological bone function. However, it is known that

humans with null alleles preventing synthesis of the $\alpha 2$ chain have connective tissue and cardiovascular abnormalities (cardiac valvular Ehlers Danlos Syndrome), without evident bone fragility.

METHODS: Col1a2 null and osteogenesis imperfecta (oim) mouse lines were used in this study and bones analysed by microCT and 3-point bending at 8 and 18 weeks. RNA was also extracted from heterozygote tissues and allelic discrimination analyses performed using qRT-PCR.

RESULTS: Mice lacking the $\alpha 2(I)$ chain (Col1a2 null) did not have impaired biomechanical or bone structural properties, unlike oim homozygous mice. The brittle bone phenotype of oim homozygotes could result from detrimental effects of the oim mutant allele, however the phenotype of oim heterozygotes is known to be less severe. We used allelic discrimination to show that the oim mutant allele is not downregulated in heterozygotes. We then tested whether gene dosage was responsible for the less severe phenotype of oim heterozygotes by generating compound heterozygotes. Data showed that compound heterozygotes had impaired bone structural properties as compared to oim heterozygotes, albeit to a lesser extent than oim homozygotes.

CONCLUSION: The presence of heterotrimeric type I collagen in oim heterozygotes alleviates the effect of the oim mutant allele but a genetic interaction between homotrimeric type I collagen and the oim mutant allele leads to bone fragility.

FUNDING: UK Medical Research Council (MR/R00319X/1)

LM3

The Col1a2 +/G610C mutation causing Osteogenesis imperfecta aggravate high-calorie diet- induced insulin resistance and bone deterioration in mice

Nitsan Nimni, Chen Dahan Abramovitch, Noam Levaot

Ben-Gurion University of the Negev, Beer-Sheva, Israel

ABSTRACT

Recent findings show that factors released by bone cells and matrix regulate energy metabolism. However, how perturbations in bone cells and matrix such as in patients with osteogenesis imperfecta (OI) affect energy metabolism is not known. To address this question, we compared bone structural parameters and metabolic parameters in a mouse model of OI under different fat-containing diets. As a model for OI we used Col1a2tm1.1Mcbr mice heterozygous for a G610C mutation in Col1a2 (OI mice). Wild type Littermates (WT) served as controls. Mice were divided into four groups according to their genotype and diet. The diet included 10% fat (lfd) and 60% fat (hfd). Eight weeks old male mice were fed with the special diets for eight weeks. OI and WT mice under hfd had similar weight which was significantly higher than the weight of lfd fed mice. High fat diet increased fasting blood glucose levels in WT and OI mice as expected, however the OI group had significantly higher levels of glucose compared to the WT group. In addition, an increase in blood insulin levels induced by hfd were more significant in OI mice than their WT counterparts. Consequently, HOMA-IR test showed that high fat diet induced more significant insulin resistance in the OI mice. To determine the effect of high calorie diet on bone structure in OI we analyzed structural parameters using microcomputed tomography. Trabecular bone volumetric fraction (BV/TV) in the vertebrae was significantly lower in OI mice compared to WT mice regardless of the diet. However, while no diet dependent effects on trabecular volumetric fraction were observed in WT mice, a significant reduction in bone volume in OI mice under high calorie diet was observed. Together our observations suggest that mice with OI are prone to develop insulin resistance and skeletal deterioration when fed with a high fat-containing diet. These observations suggest that perturbations in bone homeostasis could have implications on whole body metabolism and underline the importance of diet management in children with OI.

LM4

Osteogenesis imperfecta zebrafish models to test a new combined pharmacological approach

Francesca Tonelli¹, Cecilia Masiero¹, Valentina Daponte¹, Filippo Doria², Antonella Forlino¹

¹Department of Molecular Medicine, Biochemistry Unit, University of Pavia, Pavia, Italy. ²Department of Chemistry, University of Pavia, Pavia, Italy

ABSTRACT

OBJECTIVES: Several osteogenesis imperfecta (OI) types are characterized by intracellular retention of collagen type I, causing extracellular matrix deficiency and impaired mineralization. Although there's no definitive cure for OI, bisphosphonates are currently administered to affected individuals to limit bone resorption. Recently, the chemical chaperone 4-phenylbutyrate (4PBA) was demonstrated to increase collagen secretion *in vitro* in OI patients' and murine model cells and *in vivo* in the dominant OI zebrafish model *Chihuahua* (Chi/+). In our study, the anabolic activity of 4PBA combined with the antiresorptive property of bisphosphonate Alendronate (ALN) were tested on Chi/+ mutant fish.

METHODS: ALN toxicity was tested on wild type (WT) embryos from 1 to 7 days post fertilization (dpf) at 10, 20 and 30 μ M. Embryo coagulation, lack of somite formation, non-detachment of the tail and lack of heartbeat were evaluated. WT and Chi/+ embryos were manually dechorionated, treated from 1 to 11 dpf, then fixed and stained with Alizarin red to evaluate cranial bones mineralization level.

RESULTS: The 30 μ M dose was chosen as the higher not-toxic, but it was administered for only 5 days to avoid an impairment of osteoclastogenesis. Fish were treated from 1 to 3 dpf with 4PBA, from 4 to 8 dpf with 4PBA and ALN and from 9 to 11 dpf with only 4PBA. The combination of 4PBA and ALN increased the level of mineralization of both WT and Chi/+ cranial bones in comparison to controls.

CONCLUSION: The combination of the anabolic activity of 4PBA with the antiresorptive activity of ALN paves the way for new promising therapy for OI.

This work was supported by the Brittle Bone Societies, UK and by the "Michael Geisman" fellowship of OIF, USA.

LM5

Orbit: A Randomized, Double-Blind, Placebo-controlled, Phase 2/3 Study to Assess the Efficacy and Safety of Setrusumab in Pediatric and Young Adult Participants with Osteogenesis Imperfecta

Nicholas Bishop¹, Eric Rush^{2,3}, V Reid Sutton⁴, Luca Sangiorgi⁵, J. Oliver Semler⁶, Arun Mistry⁷, Alastair MacKinnon⁷, Claudine Woo⁸, Hui Wang⁸, Wendy Putnam⁸, Antonio Nino Ramirez⁸, Michael Ominsky⁸

¹University of Sheffield, Sheffield, United Kingdom. ²Children's Mercy, Kansas City, USA. ³University of Missouri – Kansas City School of Medicine, Kansas City, USA. ⁴Baylor College of Medicine & Texas Children's Hospital, Houston, USA. ⁵IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy. ⁶University Cologne, Cologne, Germany. ⁷Mereo BioPharma, London, United Kingdom. ⁸Ultragenyx Pharmaceutical Inc., Novato, USA

ABSTRACT

Setrusumab is a fully human anti-sclerostin monoclonal antibody being developed to treat osteogenesis imperfecta (OI). A Phase 2b study in adults with OI demonstrated robust increases in bone formation, bone density and bone strength with setrusumab across OI Types I, III, and IV (NCT03118570).

The primary objectives of the seamless phase 2/3 Orbit study (NCT05125809) are to identify a setrusumab dose strategy in Phase 2 (Ph2) and to evaluate fracture rate reduction versus placebo in Phase 3 (Ph3). The primary endpoint for Ph2 is percent change in serum P1NP after 1 month of treatment, which will help define the dose strategy for Ph3. The primary endpoint for Ph3 is annualized rate of all

radiographically confirmed fractures excluding morphometric vertebral fractures during the double-blind treatment period.

Patients aged 5 to <26 years with OI Types I, III, or IV, naïve to bisphosphonates or previously treated with bisphosphonates, a history of ≥ 1 fracture in the prior year or ≥ 2 fractures in prior 2 years, and normal serum 25-hydroxyvitamin D are being enrolled. History of skeletal malignancies, neural foraminal stenosis, or cardiovascular disease or uncontrolled endocrine diseases, hypocalcemia, or low GFR are exclusionary.

In Ph2, ~36 patients are being randomized 1:1:1 to setrusumab (low or high dose) or placebo IV monthly. In Ph3, ~195 additional patients will be randomized 2:1 to setrusumab at the dose strategy selected in Ph2 or placebo IV monthly. The primary analysis will occur between Month 12 and 24 for the last patient, as projected from fracture data collected during the study. All patients will transition to open label setrusumab after the primary analysis or Month 24, whichever comes first. Patients will not receive bisphosphonates during the study. Patients experiencing significant fractures during the treatment period will be eligible for earlier transition to setrusumab.

The Orbit study initiated in February 2022 and is currently enrolling.

LM6

Use of analgesics in patients with Osteogenesis Imperfecta in Denmark – a nationwide register-based cohort study

Camilla Jørgensen^{1,2}, Mette Wod^{3,4}, Daniel Pilsgaard Henriksen⁵, Lars Folkestad^{1,4}

¹Bone and Mineral Unit, Department of Endocrinology, Odense University Hospital, Odense, Denmark. ²Institute of Health, University of Southern Denmark, Odense, Denmark. ³Research Unit of Clinical Epidemiology, Odense, Denmark. ⁴Department of Clinical Research, University of Southern Denmark, Odense, Denmark. ⁵Department of Clinical Pharmacology, Odense University Hospital, Odense, Denmark

ABSTRACT

BACKGROUND: Osteogenesis imperfecta (OI) is a rare, hereditary disease affecting collagen type 1, which is the most abundant collagen in the human body. People with OI often experience pain, but little is known about trends in analgesic use among patients with OI.

OBJECTIVE: To investigate trends in the use of analgesics amongst people with OI in Denmark, compared to a reference population.

DESIGN: A Danish nationwide, population-, and register-based cohort study.

PARTICIPANTS: All patients registered with an OI diagnosis and a reference population matched by birth month, -year, and gender, in the period January 1977 to December 2018.

MEASUREMENTS: Prevalent analgesic users over time and by age, amount of analgesic use in Defined Daily Doses (DDD), risk of initiating analgesics during observation in Sub Hazard Ratio (SHR), and risk of initiating treatment at a specialized pain centre in SHR in the OI cohort compared to the reference population. Lastly changes in analgesic use related to fractures in the OI cohort.

RESULTS: 905 patients with OI (54% women) and 4,542 individuals in the reference population were identified. The OI cohort had more prevalent users (71.8% vs 46.8%, $p < 0.001$), which increased over time and by age. The OI cohort had significantly higher use as measured by DDDs (179.5 [IQR 40.0–979.6] vs 87.5 [IQR 28.3–342.5], $p < 0.001$). The risk of starting any analgesics was higher in the OI cohort, compared to the reference population (SHR: 1.86 [95% CI: 1.68–2.05]), and people with OI had a higher risk of starting treatment at a specialized pain centre than the reference population (2.43% vs 0.4%, SHR: 5.8 [95% CI: 3.1–11.0]). Furthermore, we found that 10% of the population accounted for @70% of the total dispensed analgesics in both groups indicating that a subgroup of people with OI experience more pain than the general OI population. The use of analgesics increased for a 60 days period after a fracture in the OI cohort. The use of tramadol, NSAIDs, paracetamol, and codeine-containing drugs increased the most after a fracture.

CONCLUSION: More people with OI use analgesics and use more analgesics, indicating more pain in the OI population than in the general population.

LM7

Rigid intramedullary nailing of lower limb segments in adolescents with metabolic bone disease

Charlene Chin See, Saeed Al-Naser, Nicolas Nicolaou, Stephen Giles, James Fernandes

Sheffield Children's Hospital, Sheffield, United Kingdom

ABSTRACT

OBJECTIVES: Metabolic bone disease encompasses disorders of bone mineralization, abnormal matrix formation or deposition and alteration in osteoblastic and osteoclastic activity. In the paediatric cohort, patients with metabolic bone disease present with pain, fractures and deformities. The aim was to evaluate the use of rigid intramedullary nailing in lower limbs in children and adolescents.

METHODS: Retrospective review was performed for an 11-year period. Lower limb rigid intramedullary nailing was performed in 27 patients with a total of 63 segments (57 femora, 6 tibiae). Majority of patients had underlying diagnoses of osteogenesis imperfecta or fibrous dysplasia (including McCune Albright disease). Mean age at surgery was 14 years. Indications for surgery included acute fractures, prophylactic stabilization, previous nonunion and malunions, deformity correction and lengthening via distraction osteogenesis.

RESULTS: All fractures healed. Correction of deformity was successfully achieved in all segments. Delayed union occurred in 4 segments in 1 patient and was successfully treated with nail dynamization. Other complications included prominence, cortical penetrance and loosening of locking screws. One patient who had lengthening performed had nonunion and was managed with exchange nailing and adjunctive measures.

CONCLUSION: Rigid intramedullary nailing is very effective in stabilisation and deformity correction of long bones in adolescent patients with pathological bone disease. The technique has low complication rates. We recommend the use of this technique in paediatric units with experience in managing metabolic bone conditions.

LM8

Chronic pain in adults with OI, its relationship with personality and the mediating role of assessment: a descriptive study

Rubén Muñoz Cortés¹, José F. Soriano Pastor², Vicente Monsalve Dolz³

¹Fundación AHUCE, Valencia, Spain. ²University of Valencia, Valencia, Spain. ³Hospital General Universitario de Valencia, Valencia, Spain

ABSTRACT

OBJECTIVES: To describe parameters and characteristics of chronic pain in a large sample of adults affected by osteogenesis imperfecta (OI). To describe the observed relationship between chronic pain and personality, daily activities and quality of life. To establish the relationship between pain appraisal and pain interference in activities of daily living and quality of life. To explore the mediating role that threat appraisal may play between pain intensity and interference with daily activities.

METHODS: Cross-sectional descriptive study of an international sample of adults affected by OI who voluntarily respond to the protocol. An online form was administered consisting of questionnaires assessing socio-demographic variables, clinical variables, pain frequency, pain intensity (EVA), personality (NEO-FFI), pain assessment (PAI), pain interference in activities of daily activities and quality of life (SF-12).

RESULTS: The sample consists of 418 people. 55% of the sample reported experiencing pain each day, increasing the percentage to 83.9% if it appeared several times a month. The areas more frequently affected by pain were the back (59.8%), pelvis and legs (22%). People who

experienced pain more frequently rated it as more intense ($p < 0.01$), saw their daily activities more affected ($p < 0.01$), and reported lower quality of life ($p < 0.01$). Participants with higher levels of neuroticism experienced pain with greater frequency ($P < .000$) and intensity ($P < .000$). Conversely, higher extraversion scores were related to a decrease in pain frequency ($P < .000$) and intensity ($P < .000$). Likewise, among people who experienced pain with high frequency, those who rated their pain as more threatening reported higher pain interference in daily activities ($p < 0.05$) and lower physical ($p < 0.05$) and mental health ($p < 0.01$). In addition, the appraisal of pain as a threat mediated between its intensity and the interference it caused in daily activities ($p < .001$).

CONCLUSIONS: Chronic pain is frequent in the adult population with OI and is problematic, interfering with daily activities and affecting quality of life. Personality traits may be a vulnerability or protective factor in relation to chronic pain. People's assessment of their own pain is also related to its impact on day-to-day physical and mental health. This opens the door to future psychological treatments that affect the appraisal that those affected make of their experience of pain.

LM9

Osteoporosis-pseudoglioma syndrome (OPPG) in two Bulgarian girls with c.2409_2503+79del mutation in LRP5 gene

Veselin Boyadzhiev¹, Milena Stoyanova², Violeta Iotova¹, Colline Collet³

¹Department of Pediatrics, Medical University, Varna, Bulgaria. ²Department of Genetics, Medical University, Varna, Bulgaria. ³Department of Genetics, Robert Debre Hospital, Paris, France

ABSTRACT

BACKGROUND: Osteoporosis-pseudoglioma syndrome (OPPG) is a rare autosomal recessive disorder characterized by severe early-onset osteoporosis and blindness. We present two girls, 16 (patient 1) and 4 (patient 2) years-of-age respectively, who presented in the clinic with the history of blindness and bone fragility started soon after birth. OPPG had been suspected and lately confirmed in both patients.

PRESENTING PROBLEM: During infancy both girls had been diagnosed with severe eye abnormalities – cataracts, microphthalmia, retinopathy and congenital blindness. First fractures took place in the second year of life. Patient 1 had sustained more than 10 fractures up to now, with moderate deformities of the chests and the limbs. Skeletal radiographs revealed generalized osteoporosis, thin “serpentine” fibulae, thoracic kyphoscoliosis, multiple spinal compression fractures (“codfish” vertebrae). Interestingly the girl also has severe psychomotor retardation – severely speech-impaired, unable to stand and walk. Patient 2 had fractured both femurs almost spontaneously at 1.5 and 2.0 years-of-age and also showed the typical radiographic signs of osteogenesis imperfecta, but has no psychomotor deficits.

CLINICAL MANAGEMENT: During the follow-up no other biochemical or imaging abnormalities had been found, both have normal internal organs. Soon after the initial admission both patients had been started on supplemental treatment with vitamin D and already had several cycles of bisphosphonates infusions with good results – no fractures since on medication therapy. Both girls are of same ethnic origin – Wallashian gypsies (“kopanari”) and live in one and the same area near the city of Varna, Bulgaria. Patient 1 has two unaffected sisters. Her parents are third cousins. In 2018 genetic analysis had been performed and revealed a homozygous c.2409_2503+79del mutation in LRP5 gene (both parents heterozygous carriers) – the diagnosis of OPPG has been confirmed. Patient 2 has no siblings and her parents did not report consanguinity. In 2022 the same mutation was found in the younger girl.

DISCUSSION: Herein we present the first two Bulgarian cases with genetically confirmed OPPG diagnose. The cognitive problems seen in the elder patient are described in only a minority of individuals with OPPG, and there are still no data that this correlates with the type of LRP5 mutation.

LM10

Microtensile properties of dry human bone extracellular matrix from individuals with Osteogenesis Imperfecta are not inferior to healthy controls

Michael Indermaur¹, Daniele Casari^{1,2}, Tatiana Kochetkova², Bettina Willie³, Johann Michler², Jakob Schwiedrzik², Philippe Zysset¹

¹ARTORG Center for Biomedical Engineering Research/ University of Bern, Bern, Switzerland. ²EMPA Swiss Federal Laboratories for Materials Science and Technology, Thun, Switzerland. ³McGill University, Montreal, Canada

ABSTRACT

Osteogenesis Imperfecta (OI) exhibits higher mineralization at the extracellular matrix (ECM) level. Recent micropillar compression experiments revealed that dry bone ECM from donors with OI do not behave in a more brittle way than the control ECM from healthy donors. Furthermore, elastic modulus and ultimate strength of OI bone ECM are not inferior compared to control and increase consistently with mineralization⁽¹⁾. However, OI may alter the mechanical behavior of the ECM in tension and the latter hypothesis is tested in this work.

In three fixed and plastic-embedded trans-iliac biopsies (control=1, OI type I=1, OI type III=1), a total of 23 microtensile specimens (c=8, OI1=7, OI3=8) were fabricated in lamellar bone using focused ion beam milling (gauge-dimension=10x5x2µm³) and were loaded in tension under vacuum⁽²⁾. During testing, force-displacement were recorded and later converted into stress-strain. After testing, fracture surface types (FST) were graded according to their fiber orientation into axial, transversal, and mixed types. Additionally, the tissue mineral density (TMD) of each biopsy was measured using µCT. A multilinear model was introduced to predict the mechanical properties with FST and TMD.

OI biopsies revealed approximately 100 mgHA/cm³ higher TMD compared to control. The failure mechanism of the tested microtensile specimens were brittle and independent of disease type. However, the OI type I biopsy revealed higher modulus and strength compared to the control and OI type III biopsies. FSTs were unevenly distributed among the biopsies. OI type III biopsy revealed no axial FST while OI type I biopsy showed mainly axial FSTs. Lastly, the multilinear model indicated that the loading modulus and ultimate strength were significantly dependent on the FST and TMD ($p < 1 \cdot 10^{-3}$).

This study is limited by the dry state of the bone, which may have a critical impact on the tensile properties especially when molecular alterations are present. Furthermore, the number of biopsies is minimal and the findings should not be overinterpreted. Nevertheless, tensile properties in combination with prior reported compression properties indicate consistently that OI bone ECM does not behave differently as compared to control bone ECM in dry conditions.

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LM11

Natural history of fractures in children and adolescents with osteogenesis imperfecta type 1: A study from Western Australia

Kiranjit Joshi^{1,2}, Richard Prince^{2,3}, Aris Siafarikas^{1,2,3}

¹Perth Children's Hospital, Perth, Australia. ²University of Western Australia, Perth, Australia. ³Western Australian Bone Research Collaboration, Perth, Australia

ABSTRACT

BACKGROUND: The natural history of the individual fracture experience of children and adolescents with OI type 1 is not well described in literature.

METHODS: In a retrospective longitudinal cohort study design, we analysed the fracture data of long bones and axial skeleton of all

paediatric patients with OI type 1, aged 0-18 years, seen at the only specialised bone clinic in Western Australia between years 2008-2020.

RESULTS: The cohort consisted of 44 patients (M=21, F=23), the median (IQR) age at time of data collection was 11.3 (6.2-17) years, giving a total of 520 patient years in the study during which 197 fractures were experienced. Although the mean fracture rate was 379 fractures per 1,000 patient years (95% CI: 310-440), the prognosis for fracture varied widely from one or less fractures in 23% (n=10) to two to twenty in 77% (n=34) of the cohort. Sex and family history of OI were not prognostic factors for fracture risk.

The highest fracture rate was observed in the age group 0-3 years at 469 fractures/1000 patient years and progressively declined to 140 fractures/1000 patient years in the age group 15-18 years. The median (IQR) age at first fracture was 1.4 (0.2-2.6) years. Regarding long bone fractures, 50% occurred in the lower limbs with the highest rate in the age group 0-3 years (331/1000 patient years, 70%) decreasing in the age group 15-18 years to 0/1000 patient years. Upper limb fracture rates increased to 307/1000 patient years in the 9-12 years group (76%) and then declined to 70/1000 years in the 15-18 years age group. Twenty-six fractures (20% of the fracture years) occurred at the same anatomical site as previous fracture. Having more than one fracture a year was significantly associated with the risk of same site fracture.

CONCLUSION: In paediatric patients with OI, fracture risk is highest in early life. The cause of the difference in the epidemiology of upper and lower limb fractures requires further work to identify correctable causes. Strategies for fracture prevention starting from young age should be one of the focuses of multidisciplinary care of children with OI.

LM12

Results of Telescopic Nailing in Children with Osteogenesis Imperfecta After Minimum Five-Year Follow-Up

Ozan Ali Erdal, Baris Gorgun, Ilker Abdullah Sarikaya, Muharrem Inan

Ortopediatri Istanbul, Istanbul, Turkey

ABSTRACT

OBJECTIVES: Telescopic intramedullary nailing (TN) has been the major fixation choice for treatment of long bone fractures or deformities in children with osteogenesis imperfecta (OI). Mid-term and long-term results are limited in the literature with controversies regarding effects on activity levels, refracture rates, and complications related to the TN devices. The purpose of the study was to evaluate results of patients at least five years after TN.

METHODS: Files of patients with OI operated for a primary TN and followed for at least five years were retrospectively evaluated. In addition to demographic data, indications for surgery, number of osteotomies required, refractures, repeat operations or additional interventions, complications and activity levels of the patients were collected.

RESULTS: 12 patients were included. 27 TN with a corkscrew tip were applied. The mean age at the index procedure was 8 years old. 23 femora, three tibiae and two humeri were operated. Most of them were done for deformity correction except three fractures, which required mean 1.3 (1-3) osteotomies. During a follow-up period of mean 73 months, 14 TN were revised in mean 21 months, while a second revision was required in five (mean 33 months). Four cases required three or more revisions after mean 46 months. The most common reason for a revision was negative telescoping of the male component (7/23). The second most common complication was nail bending due to a re-fracture (4/23). At final follow-up, six patients (50%) were independent walkers at least indoors. Rest of the cohort were walking or standing with variable support except one case who was only able to stand with support.

CONCLUSIONS: TN was found to be effective in preserving or improving activity levels of children with OI, while preventing major fractures with low complication rates.

LM13

Effects of Losartan on Transforming-Growth-Factor- β and Angiotensin pathways in Osteogenesis Imperfecta

Mai Morita¹, Diane Lefley¹, Christopher George¹, Jiabao Zhou¹, Nick Bishop^{1,2}, Penelope Ottewell¹

¹University of Sheffield, Sheffield, United Kingdom. ²Sheffield Children's NHS FT, Sheffield, United Kingdom

ABSTRACT

BACKGROUND: This study aims to understand the effects of Losartan, an angiotensin receptor blocker, on the TGF- β /Angiotensin pathways in MG63 and human OI fibroblasts. In previous mouse model experiments, low doses of losartan were effective in reducing TGF- β and bone turnover short-term and increasing vertebral bone mass long-term¹. We hypothesise losartan will increase MG63 proliferation and reduce TGF- β /Angiotensin associated gene expression.

METHODS: Proliferation and TGF- β /Angiotensin pathway associated protein expression was measured in MG63 osteoblasts, treated with 1nM, 5nM, 10nM and 20nM of losartan for 24, 48 and 72 hours. Cells were counted in triplicates using a haemocytometer. Proteins extracted from these cells were analysed by Western Blot using NF κ B primary antibodies, normalised with GAPDH and quantified with ImageJTM. To assess gene expression, cDNA synthesised from healthy and OI fibroblasts cultured under 2D and 3D conditions and treated with 1nM and 10nM of losartan will be run on RT-qPCR microfluidic cards, containing primers for 95 genes associated with the TGF- β Angiotensin pathway. Results will be analysed via QuadStudio Design and Analysis.

RESULTS: Losartan had no effect on MG63 cell proliferation across all concentrations. Qualitatively, the control cells were evenly spaced and sized, whilst the losartan-treated cells had variable size and confluency. Initial results from Western Blots identified that 72 hours following exposure to 5nM losartan was the most effective dosage to reduce NF κ B (NF κ B/GAPDH = 0.01698; 72hour 0nM = 0.34371) in MG63 cells. We are currently running human healthy and OI fibroblasts on RT-qPCR array plates to assess gene expression, and we will better understand the mechanism of action for losartan in OI.

CONCLUSION: The variability in cell size and confluency in treated cells suggests losartan impacts bone reconstruction, as opposed to growth, which is inline with existing data. 5nM losartan had the greatest effect on NF κ B production, downstream of TGF- β receptors², suggesting lower doses of losartan are most effective in reducing circulating TGF- β . The gene expression study will highlight the pathways that losartan targets in bones. Further studies of losartan in human osteoblasts, mice models and clinical trials would elucidate its extra-skeletal effects and clinical efficacy.

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LM14

Osteogenesis Imperfecta type VII: clinical variability and novel variants in CRTAP

André Travessa^{1,2}, José Carlos Rometu³, Maria João Palma⁴, Carolina Vaz-de-Macedo⁴, Silvia Modamio-Høybjør^{5,6,7}, Karen E. Heath^{5,6,7}, Ana Berta Sousa¹

¹Department of Medical Genetics and ERN-BOND, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal. ²Medical Genetics Consultation, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal. ³Department of Rheumatology and Metabolic Bone Disorders and ERN-BOND, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal. ⁴Department of Obstetrics, Hospital Garcia de Orta, Almada, Portugal. ⁵Instituto de Genética Médica y Molecular (INGEMM), Hospital Universitario La Paz, IdiPAZ, UAM, Madrid, Spain. ⁶Skeletal dysplasia Multidisciplinary Unit and ERN-BOND, Hospital Universitario La Paz, Madrid, Spain. ⁷CIBERER (Centro de Investigación Biomédica en Red de Enfermedades Raras), ISCIII, Madrid, Spain

ABSTRACT

BACKGROUND: Osteogenesis Imperfecta (OI) type VII is a moderate to extremely severe form of OI caused by biallelic variants in *CRTAP*. Until now, only about 30 cases have been reported in the literature.

Here, we report on three cases of OI type VII. Our aims are to amplify the spectrum of variants in *CRTAP* and to highlight the clinical variability of this type of OI.

CLINICAL CASES: The first case is a fetus, conceived from a Cape Verdean couple, detected to have short long bones and bowed lower limb bones and clavicles at 23 weeks gestation. The pregnancy was terminated at 25 weeks. Fetal pathology examination and X-rays suggested OI type III, and a OI panel detected the novel nonsense variant c.1020C>G p.(Tyr340*) in homozygosity in *CRTAP*.

The second case is a Cape Verdean 29-year-old woman with postnatal fractures during infancy and adolescent. She had short stature, short trunk, and bilateral genu varum. The phenotype was compatible with OI type IV, and a OI panel detected the previous variant c.1020C>G p.(Tyr340*) and the variant c.143A>G p.(Tyr48Cys), previously reported as of unknown significance, in compound heterozygosity in *CRTAP*.

The third case is a Portuguese 29-year-old woman with a total of 9 fractures, the first in the prenatal period. She walked with support since the age of 5 years. She had short stature, rhizomelic shortening, bilateral thigh and leg bowing, and scoliosis. The phenotype was compatible with OI type IV, and a skeletal dysplasia panel identified the novel variant c.471+4A>G in homozygosity in *CRTAP*, shown to have a very low population frequency and predicted to affect splicing.

DISCUSSION: Although OI type VII is invariably a moderate to severe form of OI, the phenotype is variable, ranging from prenatal cases to deforming cases with a low number of fractures and no prenatal fractures.

Here, we describe two novel variants in *CRTAP*, amplifying the spectrum of variants in this gene. One of these variants were found in one woman and one unrelated fetus with Cape Verdean ascendance, so the carrier frequency of this variant in Cape Verde population may be high.

LM15

Recurrent upper limb fractures: impact on quality of life and management challenges in two children with severe Osteogenesis Imperfecta

Emilie Hupin, Zoe Bowman-Bayles, Catherine DeVile
Great Ormond Street Hospital, London, United Kingdom

ABSTRACT

BACKGROUND: Osteogenesis Imperfecta (OI) is a genetic bone fragility disorder. Frequent fractures and long bone deformities feature in more severely affected individuals. Surgical intervention is common in the

lower limbs but there is less expertise and more complexity involved when managing the upper limbs.

Two children seen at a UK-based OI centre presented with recurrent arm fractures.

Case 1: 7-year-old male with Type 3 OI and confirmed *COLA2* gene variant presented with short stature, frequent fractures and bowing of long bones. He is a wheelchair user and can ambulate short distances with a walker.

Case 2: 5-year-old female with confirmed homozygous duplication of *WNT1* gene (Type 15 OI) presented with extreme bone fragility, vertebral compression fractures, scoliosis and bowing of long bones. She is a full-time wheelchair user, has limited floor mobility and an autistic spectrum disorder

Both children have received early treatment with bisphosphonate therapy and intramedullary rodding of lower limbs.

PRESENTING PROBLEM: Recurrent bilateral fractures of upper limbs, specifically humeri, was raised as a concern by parents. Eight fractures over a 12-month period were reported in Case 1, whilst seven fractures over a 6-month period were reported in Case 2, all occurring with low level trauma. Worsening bone deformity was identified radiologically and clinically. In both cases fractures significantly impacted on quality of life and function. School attendance, mobility and independence were all negatively affected.

CLINICAL MANAGEMENT: All fractures have been managed conservatively to date. Both cases are under Orthopaedic monitoring with management options being considered. Hard splinting was not advised in Case 1 due to bony alignment and the hypothetical risk of fracture. Case 2 previously used protective splints to minimise fracture occurrence, but use was discontinued. Intramedullary rodding is being considered but concerns regarding the technical complexity, surgical risks and potential secondary impacts on function have been highlighted.

DISCUSSION: Managing upper limb fractures, and the subsequent changes in bony alignment and function in children with severe OI can be challenging. Both conservative and surgical management options are being explored in two cases with recurrent humeral fractures. A holistic and multidisciplinary approach will be essential in any future management considerations.

LM16

Investigating mutations that cause Osteogenesis Imperfecta using molecular dynamics

Elizabeth Canty-Laird, Michael Jones
University of Liverpool, Liverpool, United Kingdom

ABSTRACT

OBJECTIVES: Osteogenesis Imperfecta is a genetic Bone Disorder caused by a variety of gene defects which affect 1 in 15,000 people. The aim of this project is to investigate the mutations within the $\alpha 1(I)$ and $\alpha 2(I)$ chains of the C-propeptide region of type I collagen. This is due to their involvement in the etiology and pathophysiology of OI. The question: "Which gene mutations have an impact on the structure and stability of type I collagen?" This is important because some mutations can halt collagen development, and some, even in the midst of continued collagen development, can give rise to dysfunctional proteins which manifests as the variants in severity seen in the OI spectrum of diseases.

METHODS: Molecular dynamics simulations were employed using a high-performance computer to study the impact that the mutations on the C-propeptide region have on the collagen structure and function. Computer software methods, such as Gromacs and PyMol, were used to act as 'molecular microscopes' that give insight into the product result of these mutations so that they can be explored. This mutation-result interface is somewhat challenging to simulate *in vivo* and so, computer simulations have proven to be a more efficient way of exploring the mutations.

RESULTS: Simulations have shown some differences between mutated structures and the normal heterotrimer. It was found that there are specific mutations that impact the structural stability and function of the

collagen. This is likely due to the unique molecular interaction between bonding sites of the different amino acids involved. The simulations revealed that mutated type I collagen C-propeptides were destabilised compared to the normal C-propeptides. The mutations impact stability by interfering with molecular forces such as the structurally important hydrogen bonds, salt bridges, disulphide bonds and Van der Waals forces. Specifically, they cause an uncontrollable loop-like structure within the petal region of the C -propeptide.

CONCLUSION: It is clear that the effects of these mutations, which results in structural discrepancies of type I collagen, can range from having very little effect to manifesting as having a severe/life-threatening impact on patient symptomatology. Molecular dynamics has no doubt advanced the way interactions between biological molecules can be observed and explored thereby providing a portal into more efficient insight surrounding disease processes.

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A focus on fractures: Understanding and addressing fracture risk in rare bone disorders



Nick Bishop¹, Peter Zioupos² and Amaka C. Offiah^{1,3}

1. Department of Oncology and Metabolism, University of Sheffield, Sheffield Children's NHS Foundation Trust, Sheffield, UK

2. Musculoskeletal & Medicolegal Research Group, Cranfield University, Defence Academy of the UK, Shrivenham, UK

3. Department of Radiology, Sheffield Children's NHS Foundation Trust, Sheffield, UK

The symposium 'A focus on fractures: Understanding and addressing the fracture risk in bone disorders', organized and funded by Mereo BioPharma plc, was held on August 31, 2022, as part of the 14th International Conference on Osteogenesis Imperfecta in Sheffield, UK.

Fractures are understood to have a significant impact on the quality of life of people with osteogenesis imperfecta (OI), and this symposium was intended to raise awareness of fractures through increasing knowledge around their origin and identification.

The symposium was chaired by Professor Nick Bishop from the University of Sheffield (UK) and featured two expert speakers, Professor Peter Zioupos from the Cranfield Forensic Institute, Cranfield University (UK) and Professor Amaka C. Offiah from the University of Sheffield (UK), who provided perspectives on the foundational origins and imaging diagnosis of fractures, respectively. Prof. Zioupos' talk explained how the biomaterial properties of bone can dictate fracture risk and how this varies based on age and disease etiology, while Prof. Offiah's talk provided an overview of the current techniques for fracture determination in bone disorders, exploring their applications and limitations.

Bone tissue properties in relation to fracture

Prof. Peter Zioupos provided the first talk of the symposium, offering a biomechanical engineer's perspective on the bone tissue properties that underlie fractures, notably the emergence of brittleness associated with conditions such as aging and OI.

Biomechanical engineers within the Musculoskeletal & Medicolegal Research Group at Cranfield University study the biomaterial properties of bone for forensic and/or anthropological applications. Through in vitro/ex vivo non-clinical investigation, information can be ascertained regarding trauma or skeletal defects (including congenital or genetic issues), environmental effects, such as exposure to toxins, and aspects of musculoskeletal performance. Such studies complement the activities of other specialties concerned with the properties of bone, such as in vivo imaging undertaken by medical physicists or in situ characterization performed by clinicians, with finite element analysis or computer modeling used to establish relationships between contexts and scales.

Fundamental to the biomechanical study of bone is the understanding that it possesses a composite, hierarchical organization, with different architectural features emergent at different scales yet working in concert to affect the structural and functional purpose of the material.¹ Accordingly, the evident composition and mechanical properties of bone depend on the scale at which it is being studied, as illustrated in Figure 1. At the *nanoscale*, organic components comprising fibrillar collagen interplay with crystalline mineral elements, defining the building blocks of bone. Observations at the *microscale* reveal higher-order architecture, with the formation of material arrangements, such as osteons and lamellae.

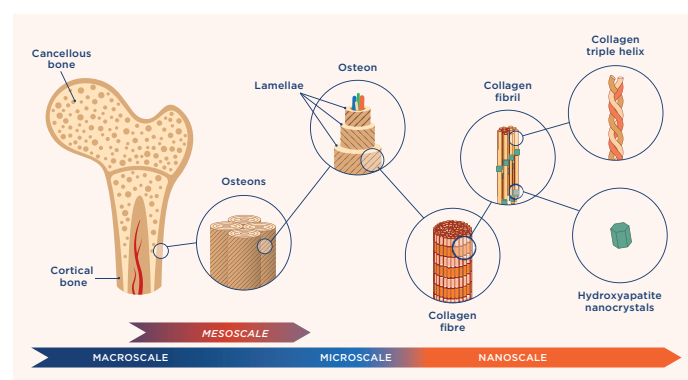


Figure 1. Scheme depicting the hierarchical organization of bone, illustrating key structural features at the macro-, micro- and nanoscales.

Finally, organization at the *macroscale* gives rise to structural elements distinguished into cortical and cancellous types of bone.¹ In studying the properties of bone, different disciplines will often map to these different structural scales in accordance with the phenomena of interest: physicists and chemists concern themselves with the molecular architecture of the (sub)nanoscale; biomechanical engineers explore the mesoscale, at the interface of micro and macrostructural properties; and physicians characterize effects emergent at the macroscale.

While it is at this latter level that fractures are managed in the clinical setting, *events* that occur at any level of bone structure may yield *effects* at any level. Therefore, a greater appreciation of the hierarchical structure of bone and the transfer of loads across bone material subunits is fundamental to understanding the nature of fractures.

At the microscale and below, bone is highly heterogeneous, and the extent of this microstructural heterogeneity is understood to have a significant influence on the formation of fractures.² Indeed, accounting for elastic mismatch between the various microstructural components of bone allows prediction of the higher-level fatigue strength of the material. The intrinsic properties of bone tissue evolve with age, both due to ontogenic and environmental influences, yielding significant changes in attributes, such as strength, stiffness and toughness. Similarly, heterogeneity increases with age, resulting in increased elastic mismatch between microstructural bone elements and an adverse effect on bone fatigue strength that is equal to or greater than factors such as mineral density or porosity.² Accordingly, heterogeneity may substantially dictate the brittleness of bone, facilitating the formation and growth of microcracks and, ultimately, leading to failure and fracture.

Given the deleterious impact of *brittleness*, demonstrated not only in the increased fracture risk through aging but also in conditions such as OI (so-called 'brittle bone disease'), contextualization of this attribute amongst the mechanical properties of bone is essential. Indeed, as bone is a natural material – complex, multifunctional and specialized – standard materials science testing and parametric definitions of strength are of limited applicability, and use of a composite rule of mixtures formulae to accommodate heterogeneity has only been partially successful.² Instead, mechanical tests are dictated by tissue type, and strength becomes a function of additional factors, such as the age and history of the tissue.³ In response, new terms, such as *damage accumulation*, have been coined to quantify aspects of bone damage.^{4–6}

Multiple phases are recognized in the fracture of bone: linear elastic deformation leading to diffuse pre-failure microcracking, slow-moving crack growth and, ultimately, catastrophic failure.⁷ In bone, the accumulating microcrack damage that precedes failure has not only been measured as yield on a stress/strain curve, but has also been detected through microscopy and acoustic emissions.⁸ A brittle material, such as glass, does not experience pre-failure damage, just a sudden catastrophic failure. Healthy bone is a semi-brittle material with some capacity for ductility; when subject to tension, the load experienced by the bone increases in a linear manner before the material yields, stretches and fails.

Being relatively non-flexible, the total deformation limit of bone is approximately 2%.⁸ Compromising the structure of bone by introducing a material inhomogeneity (e.g. a notch) can result in a significantly more brittle material; stress is concentrated at the inhomogeneity and a completely linear load curve gives way to a glass-like catastrophic fracture front. By contrast, relatively poorly mineralized antler material – a remarkable biological analog resulting from extraordinary natural evolution and adaptation – is substantially more ductile, able to accept a strain of up to 10% before failing

and not experiencing catastrophic failure even when notched.⁸ Therefore, where it matters (e.g. for survival), ductility, rather than density or stiffness, is a key factor in defining brittleness (although a lack of toughness and damage tolerance are also important, as too may be the strength of the material being measured). As previously inferred, events at the nanoscale can have effects at the macroscale, and so brittle bones observed in conditions such as OI may be traced back to bone inhomogeneity at the nanophysical level (i.e. disrupted collagen structures). Indeed, while the efficacy of drugs used to treat OI is most commonly and conveniently measured at the macroscale, the causes/effects of OI may emerge at any level depending on the scale being observed.

Compositional and material changes are observed in bone tissue as it ages, where properties such as hardness increase until around 35 years of age but then gradually decline in association with physicochemical changes, resulting in increased bone fragility.⁹ Extrinsic factors can also influence fragility; at a significantly high strain rate (high rate of deformation with respect to time), every bone is brittle.¹⁰ Moreover, aging shifts this ductile-to-brittle transition to lower strain rates such that older bones are more brittle and thus susceptible to fracture. For example, the ductile-to-brittle transition occurs at a strain rate some 10 to 40 times slower in 85-year-old cortical bone than 15-year-old cortical bone.¹¹

Nevertheless, much of the biomechanics literature is skewed towards quasi-static/slow loading materials tests rather than the fast-moving/fast-loading (high strain rate) events typically associated with real-world fracture scenarios (i.e. falls and impacts). In order to understand the origin of these brittleness effects, synchrotron X-ray scattering has been used to study events at the nanoscale, measuring mineral and collagen strain during fracture events.^{11,12} It was found that following fracture, stresses in the collagen and mineral phases relax at different rates and consequently dissociate, with the relaxation rate of collagen being on the timescale of the macroscopic ductile-to-brittle transition. Accordingly, the organic component of bone may be key to dictating the brittleness of bone, thus illuminating the heightened fracture risk in scenarios where collagen fibril formation is perturbed (e.g. OI-associated mutations).

Fracture determination in the abnormal skeleton

The second presentation was provided by Prof. Amaka C. Offiah, who compared and contrasted the various imaging modalities available for diagnosing fractures in children. The emphasis was on identifying and distinguishing inflicted injuries and underlying skeletal abnormalities, such as OI.

A proposed general approach to the diagnosis of a suspected fracture employs an age-based algorithm wherein children under the age of 2 years with no known skeletal anomaly are investigated by default under suspicion of an inflicted injury (i.e. child abuse). These investigations may include extensive radiographic survey of the entire skeleton (20–21 radiographs), a head computed tomography (CT) scan to exclude intracranial injury if less than 1 year of age and, potentially, spinal magnetic resonance imaging (MRI) depending on the results of the head CT scan. Alternatively, if the child

is known to have a skeletal anomaly, such as OI or hypophosphatasia, typically only the symptomatic site(s) should be imaged; presentation won't necessarily include pain but may instead encompass other signs, such as pseudoparalysis, swelling or abnormal angulation. For children over the age of 2 years, abuse is a less common cause of fracture,¹³ so the investigation should focus on the imaging of symptomatic site(s) whether or not there is knowledge of an existing skeletal condition. Signs of skeletal abnormality evident during imaging may aid the diagnosis of any underlying disorder, whereas the type and circumstances of the fracture may raise suspicion of child abuse.

As summarized in Table 1, various modalities are available for skeletal imaging and the diagnosis of fractures in children, each with their advantages, disadvantages and preferred applications. The most common technique, conventional radiography "X-ray", benefits from wide availability and accessibility of relevant expertise and equipment, relative ease of performance and interpretation and comparatively low costs. Fracture dating can be relatively straightforward using conventional radiography, and the technique may provide a general overview of proportions in small children (to aid, for example, in the diagnosis of skeletal dysplasia). Conventional radiography may also be used to observe periosteal reaction in physiological or pathological conditions; the former being observable for up to 8–9 months of age (in digital radiographs) and the latter encompassing trauma, such as fracture, as well as conditions including osteomyelitis, rickets, scurvy, hypervitaminosis A and neuroblastoma.¹⁴

In diaphyseal fractures, periosteal reaction and callus (soft or hard) are signs of healing, and in children with OI, a review of existing radiographs (along with a history provided by the child's parents) may be beneficial in determining whether the symptoms (e.g. pain) are due to a new fracture or other cause at the site of a healing fracture. Conversely, metaphyseal fractures, typically associated with inflicted injury¹⁵ and rare in OI¹⁶, do not heal with a periosteal reaction, which (if seen in association with metaphyseal fractures) arises due to stripping of the periosteum at the time of fracture. Accordingly, the presence of a periosteal reaction can be used to date metaphyseal fractures.

A key drawback of conventional radiography is its relatively low diagnostic accuracy for fractures of certain bones (e.g. the ribs, metaphyses and, in some instances, the skull). In certain fractures, follow-up radiographs may be necessary to accommodate this low diagnostic accuracy, especially in the context of suspected abuse, thus necessitating additional exposure to a relatively high radiation dose. Whole-body radiography imparts a mean radiation dose of approximately 0.20 mSv,¹⁷ roughly the equivalent of 1 month of typical background radiation in the UK;¹⁸ mean effective doses experienced during whole-body imaging using the other modalities discussed range from 0 mSv for methods that do not employ ionizing radiation (MRI and ultrasound), up to 0.001 mSv for dual X-ray absorptiometry (DXA),¹⁹ 2.3 mSv for nuclear medicine imaging¹⁷ and 4.8 mSv for a low-dose CT.²⁰

CT provides cross-sectional imaging generated from multiple X-ray measurements at different angles, facilitating multiplanar examinations and three-dimensional (3D) reconstructions. The technique is

relatively rapid – a whole-body CT scan can be performed in the duration of a single breath-hold (compared with 30 minutes or more for a conventional radiographic skeletal survey), but whole-body CT scans are not commonly performed and, therefore, CT is not used to provide an overview of proportions. However, CT imaging provides a useful diagnostic tool for fracture identification in bones that prove difficult for conventional radiography. For instance, a head CT obviates the need for skull radiographs and provides greater diagnostic accuracy, especially when utilizing 3D reconstructions.²¹ Similarly, over 80% of acute rib fractures are missed on conventional radiographs, even proving difficult to identify when referring back to chest radiographs after locating fractures using CT.^{22–24}

Multiplanar 3D reconstruction and software capable of visualizing the standard 3D rib arc reconstruction as a grid may aid in the identification of rib fractures. Given the apparent advantages of CT in diagnosing rib fractures and the likelihood that multiple chest radiographs will likely infer a higher radiation dose than a single CT, a potential role for routine CT chest imaging in children may exist.²⁵ In order to address this, a multicenter study (RECEPTOR) is underway in 20–30 centers across Europe to understand whether CT is indeed a better first-line tool for the diagnosis of rib fractures in suspected abuse than a set of initial plus follow-up radiographs. Other notable roles for multiplanar 3D CT reconstruction include the diagnosis of traumatic acetabular fractures and vertebral fractures that may be obscured by skeletal deformities, such as OI-emergent severe scoliosis. Disadvantages of CT include the high associated radiation dose, lower availability/accessibility than conventional radiography and high associated costs. Additionally, CT may be inferior to conventional radiology in imaging periosteal reaction (only 32% of periosteal reaction seen on conventional radiographs can be identified on CT) and healing fractures look substantially different in 3D CT reconstructions than they do on radiographs.²⁶

Nuclear medicine, such as positron-emission tomography (PET), can provide whole-body imaging with high specificity at a lower ionizing radiation dose than CT. While reportedly having greater sensitivity than a gold standard radiography skeletal survey for the overall detection of fractures, especially rib fractures, PET has a lower sensitivity in the detection of metaphyseal fractures. Because metaphyseal fractures are characteristic of child abuse, distinguishing suspected inflicted injuries from those arising due to skeletal abnormalities still necessitates a radiographic evaluation.²⁷ Several other factors, including a relatively high ionizing radiation dose and limited availability of radioisotopes and appropriate equipment/personnel, make PET less favorable for the diagnosis of fractures in children. Similarly, whole-body scintigraphy (bone scan) is reasonably sensitive and may have applications in adults or niche diagnoses (e.g. stress fractures around the pelvis), but growth plates give a particularly high signal,²⁸ so the technique may obscure metaphyseal fractures in children.

Like CT, MRI offers multiplanar whole-body imaging, but avoids ionizing radiation and has excellent contrast resolution. As with CT, multiplanar imaging makes MRI amenable to diagnosing vertebral fractures in cases of spinal deformity. Additionally, the so-called 'black bone' MRI technique and 3D reconstruction may provide high sensitivity and selectivity for skull fractures, making it

Table 1: Advantages and disadvantages of fracture determination modalities in children

Imaging modality	Advantages	Disadvantages	Favored applications
Radiography	<ul style="list-style-type: none"> • Widely available/accessible • Relatively low cost • Relatively easy to perform • Relatively easy to interpret <ul style="list-style-type: none"> – Including fracture dating • General overview of proportions (smaller children) 	<ul style="list-style-type: none"> • Relatively high radiation dose • Relatively low diagnostic accuracy for fractures of: <ul style="list-style-type: none"> – Ribs – Metaphyses – Skull (some instances) 	<ul style="list-style-type: none"> • Mainstay of fracture diagnosis in children with or without an underlying condition
CT	<ul style="list-style-type: none"> • Multiplanar <ul style="list-style-type: none"> – 3D reconstructions • Quick 	<ul style="list-style-type: none"> • High radiation dose • Not widely available/accessible • Relatively high cost • No overview of proportions (whole body CT not commonly performed) 	<ul style="list-style-type: none"> • Accurate diagnosis of skull fractures (head injury) and traumatic acetabular fractures • Troubleshooting rib fractures • Diagnosis of vertebral fractures in the presence of severe scoliosis • Guiding orthopedic intervention
Nuclear medicine	<ul style="list-style-type: none"> • Whole body • Sensitivity • High specificity (PET) 	<ul style="list-style-type: none"> • High radiation dose • Non-specific (bone scan) • Not readily available <ul style="list-style-type: none"> – Radioisotope – Equipment – Personnel 	<ul style="list-style-type: none"> • Diagnosis of pelvic stress fractures (bone scan)
MRI	<ul style="list-style-type: none"> • Whole body • Multiplanar • Excellent contrast resolution • No ionizing radiation 	<ul style="list-style-type: none"> • High cost • Reduced availability/accessibility • Time consuming • May require sedation/general anesthesia 	<ul style="list-style-type: none"> • Evaluating neurological complications • Complementing skeletal surveys with the identification of soft tissue abnormalities • General troubleshooting (where sedation is not required) • Diagnosis of vertebral fractures in the presence of severe scoliosis
Ultrasound	<ul style="list-style-type: none"> • Portable • No ionizing radiation • High resolution • Relatively low cost 	<ul style="list-style-type: none"> • Time consuming • Localized imaging 	<ul style="list-style-type: none"> • Troubleshooting of equivocal radiographs, especially in identifying metaphyseal fractures
DXA	<ul style="list-style-type: none"> • Low radiation dose • Relatively quick 	<ul style="list-style-type: none"> • Limited availability of equipment/trained personnel • Limitations of pediatric VFA/MXA 	<ul style="list-style-type: none"> • Vertebral fracture assessment • Quantitative morphology (spinal deformation)

a potentially viable alternative to CT.²⁹ Nevertheless, the limited availability/accessibility and high costs of the technique limit its utility, as does the relatively long image acquisition time, which may necessitate sedation depending on the age of the child. Moreover, MRI is insensitive to metaphyseal and rib fractures, although higher magnetic field strengths and improved radiofrequency coils may improve diagnostic accuracy.³⁰

Ultrasound is another modality capable of imaging fractures at high resolution without the use of ionizing radiation but with the added advantages of being portable and low cost. However, ultrasound provides only localized imaging, requiring each site to be scanned independently (e.g. rib by rib), thus making the process potentially time consuming.³¹ One particularly promising application of ultrasound is the confirmation of metaphyseal fractures, for which the technique has high specificity.³²

Finally, a number of emerging modalities are receiving particular attention for the assessment of vertebral fractures, a significant complication of OI and strong indicator of bone fragility.³³ One such example is DXA, which has a lower radiation dose and equivalent diagnostic

accuracy to conventional radiographs.^{34–36} Vertebral fracture assessment (VFA) data have also been coupled with artificial intelligence to provide morphometric VFA (MXA), semi-automated software-based vertebral fracture identification intended to minimize inter- and intra-observer variability; however, an appropriate pediatric standard is required to bolster the reliability of this method.^{33,37,38}

Another such method is the EOS imaging system, which acquires perpendicular, biplanar scans of the patient to generate a hollow 3D surface image. As it can image a standing child relatively quickly with a radiation dose comparable to DXA, EOS has the capability to aid in the identification of fractures, particularly vertebral, but is not commonly in first line use in clinical practice for this indication.

Conclusion

While of interest to the understanding of fractures more generally, this symposium was of particular relevance within the context of OI as it explored the root cause of bone brittleness and preferred modalities for diagnosing fractures in children. Fractures represent a substantial burden to people with OI, regardless of phenotype or genotype, and a greater focus on addressing their origins and management is essential to improving the quality of life of people with OI.

Through perspectives from the fundamental to clinical domains of study, we can appreciate the multiple levels of exploration that are key to understanding fractures, mirroring the hierarchical structure of bone itself.

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CONFLICTS OF INTEREST

NB is global chief investigator for Mereo's study of setrusumab in OI, is a member of the setrusumab advisory board and has undertaken speaking commitments for both Mereo and Ultragenyx. He has also served as principal investigator for Alexion in studies of hypophosphatasia and Amgen in studies of denosumab in OI. He has consulted for Alexion, Amgen, Novartis, UCB and Kyowa Kirin and served on advisory boards for Alexion and Internis. For his participation in the symposium, PZ has received consulting fees from Mereo, paid to his institution. ACO has received grants and honoraria from Alexion, BioMarin, Mereo and InfoMed.