13th International Conference on Osteogenesis Imperfecta

PROGRAMME & ABSTRACTS

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Pega Medical
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Programme & Abstracts

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- Andreas Henden
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- Ingunn Westerheim – Conference Coordinator

Meeting organisation

- Norwegian Osteogenesis Imperfecta Association (NFOI)
- Gyro AS

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## Overview Programme

### Programme: Sunday August 27th

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>17:00 - 17:20</td>
<td>Welcome address</td>
</tr>
<tr>
<td>17:20 - 18:45</td>
<td>Keynote lectures</td>
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<tr>
<td>18:45 - 20:00</td>
<td>Welcome Reception</td>
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<td></td>
<td>EXPO HALL FOYER</td>
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<td><em>Followed by free time</em></td>
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### Programme: Monday August 28th

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<tr>
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<tr>
<td>09:00 - 09:15</td>
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<td>Session 1 Genotype - Phenotype - Diagnosis</td>
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<td>11:30 - 13:00</td>
<td>Session 2 Collagen: mutations and altered modification</td>
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<td><em>Lunch is served in Brasserie X, the hotel restaurant.</em></td>
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<td>14:00 - 15:00</td>
<td>Session 3 Debate: &quot;This house believes that stem cell transplant is the optimal treatment of OI”</td>
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<td>Session 4 Orthopaedic Developments</td>
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<td>Bone Tissue in Human OI, Mice and Z-fish models</td>
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<td>WS3</td>
<td>Orthopaedic techniques (in parallell with session 8) – <em>Idérommet</em></td>
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Scientific Programme  
August 27th - 30th 2017  

ALL SESSIONS ARE IN EXPO HALL UNLESS OTHERWISE INDICATED

Programme: **Sunday August 27th**

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| 17:00 - 17.20 | **Welcome address**  
Chairs: Lena Lande Wekre (Programme Chair)  
Inger-Margrethe Stavdal Paulsen (Chair of NFOI) |
| 17:20 - 18.45 | **Keynote lectures**  
17.20 - 18.00 | Biomimicry – could it help us find novel treatment strategies for human disease?  
Peter Stenvinkel (Stockholm, Sweden)  
18.00 - 18.40 | The Role of the Osteocyte in Muscle/Bone Crosstalk  
Lynda Bonewald (Kansas City, US) |
| 18.45 - 20.00 | **Welcome Reception**  
EXPO HALL FOYER  
Followed by free time |

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Moderator: David Sillence (Sydney, Australia)  
Invited speaker: Paul Coucke (Ghent, Belgium):  
Further insights in the pathogenetic mechanism of OI through human and zebrafish |
Oral Communications

O1
Growth Characteristics in Osteogenesis Imperfecta – Results from an Observational Study from the Linked Clinical Research Centers and the Brittle Bone Disorders Consortium
Vernon Reid Sutton, Houston, US

O2
Longitudinal Growth Curves for OI Caused by Structural Mutations in Type I Collagen
Joan Marini, Bethesda, MD, US

O3
A familial FKBP10 mutation associated with a wide phenotypic spectrum ranging from Arthrogryposis to OI
Osama Essawi, Ghent, Belgium

11.00 - 11.30
Coffee break

11:30 - 13:00
Session 2   Collagen: mutations and altered modification
Moderator: Joan Marini (Bethesda, US)

Invited speaker: Ruud A Bank (Groningen, The Netherlands)
Molecular insights into lysyl hydroxylation and cross-linking of fibrillar collagens in normal and diseased bone

Invited speaker: Richa Garva (Manchester, UK)
The clock ticks for collagen

Oral Communications

O4
Use of patient-specific iPSCs as a platform for genotype-phenotype analysis of OI
Xiaonian Xin, University of Connecticut, US

O5
SPARC-related osteogenesis imperfecta with a myopathy-like presentation
Cecilie Rustad, Oslo, Norway

O6
Biochemical characterization of a COL1A1 signal peptide heterozygous mutation leading to severe OI
Uschi Lindert, Zurich, Switzerland

O7
Chemical chaperone treatment ameliorates cellular homeostasis of patients with Osteogenesis Imperfecta
Antonella Forlino, Pavia, Italy

13:00 - 14:00
Buffet lunch/Exhibits/Posters
Lunch is served in Brasserie X, the hotel restaurant.
### Session 3

**Debate:** "This house believes that stem cell transplant is the optimal treatment of OI"

**Moderator:** Bente Lomholt Langdahl (Århus, Denmark)

**Invited speakers:**
- Cecilia Götherström (Stockholm, Sweden)
- Nick Bishop (Sheffield, UK)

#### 15.00 - 15.30 Coffee break

### Session 4

**Orthopaedic Developments**

**Moderator:** Richard Kruse (Wilmington, DE, US)

**Invited speaker:** Thomas Wirth (Stuttgart, Germany)

**Surgery in upper extremities in OI**

### Oral communications

<table>
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<tr>
<th>Session</th>
<th>Title</th>
<th>Speaker(s)</th>
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<tr>
<td>O8</td>
<td>Incidence and treatment of femur fractures in adults with Osteogenesis Imperfecta</td>
<td>Alexander Goudriaan, Zwolle, The Netherlands</td>
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<td>O9</td>
<td>Challenges of treating the tibia in patients with osteogenesis imperfecta. A single surgeon series</td>
<td>Darko Anticevic, Zagreb, Croatia</td>
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<tr>
<td>O10</td>
<td>Results of combined intramedullary nailing and supplemental fixation of long bones in patients with osteogenesis imperfecta (OI)</td>
<td>Matthias Rogalski, Berlin, Germany</td>
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<tr>
<td>O11</td>
<td>Management of the Upper Extremity in OI: 20+ years’ experience</td>
<td>Kathleen Montpetit &amp; Francois Fassier, Montreal, Canada</td>
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<tr>
<td>O13</td>
<td>Acetabular Protrusio in Osteogenesis Imperfecta: Progression and Risk Factors</td>
<td>Junho Ahn, New York, US</td>
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<tr>
<td>O14</td>
<td>Prevalence and progression of spondylolistheses in children with Osteogenesis Imperfecta</td>
<td>Verity Pacey, Macquarie University, Australia</td>
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### 17.30

**Social programme (faculty dinner & sightseeing tour for participants)**
Programme: **Tuesday August 29th**

**09:00 - 09:15**  **Opening remarks**

**09:15 - 11:00**  **Session 5  The Connective Tissue Spectrum in OI**  
**Moderator:** Jannie Dahl Hald (Århus, Denmark)

**Invited speakers:**
Lars Folkestad (Odense, Denmark)  
Cardiovascular diseases in patients with Osteogenesis Imperfecta – a nationwide, register-based cohort study

Barbro Malmgren (Stockholm, Sweden)  
Tooth agenesis in osteogenesis imperfecta; prevalence, mutations and therapeutic considerations

Hollis Chaney (Washington, US)  
Pulmonary Complications of Osteogenesis Imperfecta

**Oral Communications**

**O15**  
**Scoliosis and Cardiopulmonary Outcomes in Osteogenesis Imperfecta**  
Cathleen Raggio, New York, US

**O16**  
**Dental occlusion and temporomandibular disorders in adults with osteogenesis imperfecta**  
Hans Gjørup, Aarhus, Denmark

**11.00 - 11.30**  **Coffee break**

**11:30 - 13:00**  **Session 6  Bone Tissue in Human OI, Mice and Z-fish models**  
**Moderator:** Peter Byers (Seattle, US)

**Invited speaker:** Nadja Fratzl-Zelman (Vienna, Austria)  
Bone material characteristics in human Osteogenesis imperfecta (OI) and mouse models

**Oral communications**

**O18**  
**Collagen C-propeptide Cleavage Deficiency Increases Bone Mineralization and Alters Bone Cell Differentiation**  
Aileen Barnes, Bethesda, MD, US

**O19**  
**Altered Bone Nano- and Microstructure in Osteogenesis Imperfecta caused by a C-propeptide Cleavage site Mutation**  
Jannie Dahl Hald, Aarhus, Denmark
**O20**
Murine model for type VI OI (Serpinf1-/-) reveals dynamic regulation of vascularization and mineralization in bone
Heeseog Kang, Bethesda, MD, US

**O21**
Zebrafish type I collagen mutants show a spectrum of skeletal phenotypes mimicking the clinical variability in OI
Andy Willaert, Ghent, Belgium

**13:00 - 14.00**
**Buffet lunch/Exhibits/Posters**
*Lunch is served in Brasserie X, the hotel restaurant.*

**14:00 - 15:25**
**Session 7**
**Current status in treatment** - *Expo Hall 2 + 3*
Moderator: Francis Glorieux (Montreal, Canada)

*Invited speaker: Brendan Lee (Texas, US)*
Implications of Excessive TGFb signaling in Collagen-related forms of OI on Treatment

**Oral communications**

**O23**
Combined effects of sclerostin antibody and pamidronate induce distinct advantages for OI treatment in Brlt/+ mouse
Ken Kozloff, Ann Arbor

**O24**
Cathepsin K knockout reduces fracture incidence and improves trabecular bone mass and microarchitecture in the axial skeleton of oim/oim mice
Thomas Roels, Brussels, Belgium

**O25**
Screening for osteogenic compounds using the zebrafish as a model
Jan Willem Bek, Ghent, Belgium

**15.25 - 15.45**
**Coffee break**

**O22**
Generation of recessive osteogenesis imperfecta zebrafish models using CRISPR-Cas9 system
Francesca Tonelli, Pavia, Italy

**O26**
Characterization of Chihuahua as a dominant osteogenesis imperfecta zebrafish model and its use in new pharmacological approaches
Antonella Forlino, Pavia, Italy

**O27**
Use of induced pluripotent stem cells and CRISPR/Cas9 in Osteogenesis Imperfecta: first results
Fleur van Dijk, Groningen, The Netherlands
15:45 - 17:05
Parallell workshops

**WS1. Unmet needs in preclinical/animal research (basic) - Idérommet**
Moderator: Oliver Semler (Cologne, Germany)

*Introduction to discussion: Chris Niyibizi (Hershey, US):*
Animal models of osteogenesis imperfecta and their application in testing novel therapies

**Debate**

**WS2. Follow up in OI – all ages (clinical) - Expo Hall 2 + 3**
Moderator: Eva Åström (Stockholm, Sweden)

*Introduction to discussion: Francis Glorieux (Montreal, Canada) – children*
*Lars Folkestad (Denmark) / Lena L. Wekre (Norway) – adults*

**Debate**

17.05 - 17.30
Coffee break

17:30 - 18:30
Session 8 Rehabilitation /Pain /Quality of life (in parallell with Workshop - Orthoepadic techniques) - Expo Hall 2 + 3
Moderator: Lena Lande Wekre (Oslo, Norway)

**Oral communications**

O28
*Physical activity levels and perceived barriers to participation of children with Osteogenesis Imperfecta*
Verity Pacey, Macquarie University, Australia

O30
*Osteogenesis Imperfecta Foundation: New Strategies in Advancing Education of Individuals, Families and Healthcare Providers*
Tracy Hart, Gaithersburg, US

O31
*Preventative Care and Treatment in Osteogenesis Imperfecta: What role for Clinical Psychology?*
Megan Riddington & Rebecca Jones, London, UK

17:30 - 18:45
**WS3 - Orthopaedic techniques (in parallell with session 8) – Idérommet**
Moderators: Ivan Hvid (Oslo, Norway) & Thomas Wirth (Stuttgart, Germany)

*Introductions to discussion:*
Francois Fassier (Montreal, Canada)
Miguel Galban (Medellín, Colombia)
Darko Anticevic (Zagreb, Croatia)
Inger Holm (Oslo, Norway)

20:00 - 23:00 **Aperitif & Conference dinner**
*Aperitif is served in the Reception Bar. Conference dinner is served in Expo Hall.*
Programme: **Wednesday August 30th**

**09:00 - 09:15 Opening remarks**

**09:15 - 10:45**
**Session 9** New genes for OI
Moderator: Antonella Forlino (Pavia, Italy)

*Invited speaker: Joan Marini (Bethesda, MD, US)*
What is Osteogenesis Imperfecta (OI) in 2017?

**Oral communications**

**O32**
Insights into bone phenotype and collagen biochemistry of TMEM38B null mutations causing Type XIV OI
Nadja Fratzl-Zelman, Vienna Austria

**O33**
Severe Osteogenesis Imperfecta presentation in a family with a novel CREB3L1 mutation
Dimitra Micha, Amsterdam, The Netherlands

**O34**
Defective Regulated Intramembrane Proteolysis (RIP) due to mutations in MBTPS2 underlies X-linked Osteogenesis Imperfecta (OI), Joan Marini, Bethesda, MD, US

**O35**
FAM46A mutations are responsible for autosomal recessive form of Osteogenesis Imperfecta
Valerie Cormier-Daire, Paris, France

**10.45 - 11.10**
**Coffee break**

**11.10 - 11.30**
**Patient Organisations**
Ingunn Westerheim (OIFE) & Tracy Hart (OIF)
The role of the patient organisations

**11:30 – 12:30**
**Session 10** Consortia in OI
Moderator: Nick Bishop (Sheffield, UK)

*Invited speaker: Luca Sangiorgi (Bologna, Italy)*
European Reference Network for Rare Bone Disorders, ERN – BOND

*Invited speaker: Vernon R. Sutton (Texas, US)*
“The American way” - Brittle Bone Disorders Consortium

**Debate**

**12.45 - 13.00**
**Closing and final remarks**
Announcement of the 14th International conference on OI

**From 13.00**
Grab & Go Lunch
PROGRAMME CHAIR

Lena Lande Wekre
Lena Lande Wekre, MD, PhD is Chair of the Organizing Committee of OIOslo2017 and member of the Scientific Committee. Dr. Wekre is a Special Advisor in medicine at the Norwegian National Advisory Unit on Rare Disorders as well as a Senior Consultant at TRS National Resource Centre on Rare Disorders. She has been working in the field of rare disorders since 1999, especially with connective tissue disorders and skeletal dysplasias. As part of her PhD, she conducted a population-based study on adults with OI, which has formed the basis of follow-up routines for this group. Dr. Wekre is representing Norway in the EU initiated project on rare Disorders, RD-action.

KEYNOTE SPEAKERS

Peter Stenvinkel
Peter Stenvinkel (MD) became a specialist in nephrology in 1992 and has a doctoral degree in renal medicine from 2004 at Karolinska Institutet, Stockholm, Sweden. In 1997 he became an Associate Professor (Docent) at the same institute, where he has been working as a full professor since 2009. His work is divided between 70% research and administration and 30% clinical duties. He’s a senior lecturer at Karolinska University Hospital. He was serving as a Visiting Associate Professor at University of California Davis, USA from 2000-2001 and a Visiting Professor in Perth Australia in November 2013.

Lynda Bonewald
Dr. Bonewald is the Director of the Indiana Center for Musculoskeletal Health. She received her Ph.D. in Immunology/Microbiology from the Medical University of South Carolina, was promoted from Assistant to Full Professor at the Univ. of Texas Health Science Center and served as director of the Bone Biology Research Program and Vice Chancellor for Research at the University of Missouri-Kansas City. She is a Past-President of the ASBMR and ABRF. She has served as Chair of the Board of Scientific Councilors for the NIDCR and served on Council for NIAMS. She is best known for her work in the study of osteocyte biology and function.

INVITED SPEAKERS

Paul Coucke
Paul Coucke, PhD, is the supervisor of the Heritable Connective Tissue Disorders lab (HCTD) (ISO 15189) at the Center for Medical Genetics Ghent (CMGG) since 2001. He is also involved in the HCTD research where he leads the technology development program of the research group. Recently, he set up a zebrafish facility within the department. He is assistant professor at the Ghent University and author of over 190 peer-reviewed papers and trained over 20 Master students and 6 PhD students. A recent analysis on his publications in the citation report reveals > 3,800 citations, on the average 30 citations per publication and his h-index is 35 (ISI).
Ruud A Bank
Ruud Bank (1960) received his Ph.D. in 1993 at the Vrije Universiteit (Amsterdam) for his work on post-translational modifications and genetics of the isozymes of amylase and pepsinogen in humans. In 1993 he started as a postdoc at TNO Quality of Life (Leiden), where he investigated the role of the collagen network in connective tissue diseases (osteoarthritis, osteogenesis imperfecta, Bruck syndrome, osteoporosis, fibrosis). In 2009 he became full professor in the field of Matrix Biology and Tissue Repair at the University Medical Center Groningen. He co-founded in 2000 the Dutch Society for Matrix Biology.

Richa Garva
Richa Garva is a postdoctoral associate in Karl Kadler’s laboratory. His lab in the Wellcome Trust Centre for Cell-Matrix Research at the University of Manchester aims to understand how cells synthesize and maintain connective tissues. They have shown that matrix synthesis occurs at the plasma membrane during embryonic development. However, how cells maintain the matrix during adult life is unknown. His group has recently shown that the circadian clock regulates the synthesis and removal of matrix on a daily basis to service the loading regimes of tissues. The implications for tissue ageing and disease will be the topic of her seminar at the Oslo 2017 meeting.

Cecilia Götherström
Cecilia Götherström is Associate Professor of Stem Cell Research at Karolinska Institutet and her research is in the field of perinatal regenerative medicine. She was one of the first in the world to isolate and characterize human fetal mesenchymal stem cells. Dr Götherström has developed fetal mesenchymal stem cells for prenatal and postnatal transplantation purposes and since then, the cells have indeed been used clinically to treat fetuses and children suffering from severe osteogenesis imperfecta with promising results. Dr Götherström is leading an international multicentre trial called BOOSTB4 to evaluate the clinical effect of mesenchymal stem cell transplantation in the treatment of severe osteogenesis imperfecta.

Nick Bishop
Professor Nick Bishop is an internationally recognised expert in the field of paediatric bone research with a particular focus on EM/early phase studies in osteogenesis imperfecta, steroid-induced or disease-associated osteoporosis and hypophosphatasia, as well as an interest in early life influences on later skeletal health. He is based at Sheffield Children’s Hospital, a member of the BOND Rare Bone Disease ERN, and the lead designated centre for the nationally-commissioned Highly Specialised Severe, Complex and Atypical Osteogenesis Imperfecta Service. He is an Associate Director of the AR-UK Experimental Arthritis Treatment Centre, leading the bone theme, President of the Academic Paediatric Association of Great Britain and Ireland and Director of the Clinical Research Facility at Sheffield Children’s Hospital.
**Thomas Wirth**

Thomas Wirth, MD, PhD is currently Director of the Department of Orthopaedics at the Olgahospital in Stuttgart, one of the largest paediatric hospitals in Germany and is Professor of Orthopaedic Surgery at the Philipps University of Marburg. He is the Past President of the German Association of Paediatric Orthopaedics, Treasurer of EPOS (2012-2016) and was elected 2nd Vicepresident of EPOS in May this year. He is a member of the International Paediatric Orthopaedic Think Tank (IPOTT). In 2014, he was awarded the Golden Honorary Needle of the German Society of Orthopaedics and Orthopaedic Surgery (DGOOC) in recognition of his contribution to Paediatric Orthopaedics. He has an active research interest in the basic science of the growth plate, paediatric hip disorders, paediatric trauma and the use of arthroscopy in children’s orthopaedics. His main clinical work furthermore includes the treatment of children with skeletal dysplasias, osteogenesis imperfecta, spine disorders and benign and malignant bone tumours.

**Lars Folkestad**

Lars Folkestad is currently finishing his post graduate specialist training to become an adult endocrinologist. He defended his phd thesis entitled Morbidity and Mortality in Patients with Osteogenesis Imperfecta in Denmark earlier this year at the University of Southern Denmark, Department of Clinical Research. Lars has been a member of the Bone and Calcium Metabolic Diseases Research Unit at the Endocrine Elite Research Centre – Department of Endocrinology and Metabolism, Odense University Hospital, since 2005.

**Barbro Malmgren**

Barbro Malmgren is a specialist in Paediatric Dentistry and has served as Senior Consultant with responsibility for the post-graduate training in Paediatric Dentistry at the Eastman Institute, Stockholm. In 1991 she joined the Swedish national multidisciplinary pediatric OI team, and in 2004 she was promoted Medical Doctor, PhD, by Karolinska Institutet. The name of her thesis is “Clinical, Histopathologic and Genetic Diagnosis in Osteogenesis Imperfecta and Dentinogenesis Imperfecta”. She has a current position as supervisor for PhD-students at the Karolinska Institutet.

**Hollis Chaney**

Hollis (Holly) Chaney, MD earned her bachelor’s degree from the University of California at Riverside. She received her medical degree from the Medical College of Pennsylvania. Dr. Chaney completed both her internship and residency in Pediatrics at Kaiser Foundation Hospital in California. After her residency, she completed a Pediatric Pulmonary Medicine fellowship at Children’s Hospital of Pittsburgh. Dr. Chaney is an Assistant Professor in Pediatrics at The George Washington University School of Medicine and Health Sciences. Dr. Chaney is the Vice Chair of the Division of Pulmonary Medicine at Children’s National Health System. She is board certified in pediatric pulmonary. Dr. Chaney has been practicing in Children’s Division of Pulmonary Medicine for over 25 years. She is particularly interested in Cystic Fibrosis and skeletal dysplasia.
Nadja Fratzl-Zelman
Nadja Fratzl-Zelman is Senior Research Associate at the Ludwig Boltzmann Institute of Osteology in Vienna Austria, where she has been working since November 1987. She holds a PhD in Biology from the University of Vienna (1986) with the specializations Plant Physiology, Organic Chemistry and Human Biology. Her research interests include bone cell biology, as well as bone material quality in genetic and metabolic bone diseases. Recently she has been working on characterizing bone matrix and mineral properties in classical and in new forms of Osteogenesis imperfecta. Since 2016, she is also member of the executive committee of the Austrian Bone and Mineral Society.

Brendan Lee
Dr. Lee is Professor and Chairman of the Department of Molecular and Human Genetics at Baylor College of Medicine. Dr. Lee has been recognized by election to the National Academy of Medicine, Fellow of the American Association for the Advancement of Science (AAAS), the Association of American Physicians (AAP), the American Society for Clinical Investigation (ASCI), and the Society of Pediatric Research (SPR). Recently, he has also been awarded the ASHG Curt Stern Award for Outstanding Scientific Achievement. Dr. Lee was an Investigator of the Howard Hughes Medical Institute prior to his appointment as Chair in 2014.

Chris Niyibizi
Dr. Niyibizi is an Associate Professor of Orthopaedics and Rehabilitation and Biochemistry and Molecular Biology at Penn State College of Medicine, Hershey PA. Dr. Niyibizi received his MSc. Degree in Biochemistry from Rutgers University and PhD in Biochemistry in the division of Experimental Medicine at McGill University in Montreal Canada under the direction of Dr. Michel Van Der Rest. After completing his Ph.D. studies, Dr. Niyibizi pursued postdoctoral fellowships at Harvard Medical School and University of Washington in Seattle where he continued his studies in Collagen Biochemistry and the pathologies that result from them under direction of Dr. David Eyre. After completing his postdoctoral studies he took a faculty position at the University of Pittsburgh and continued his studies on connective tissue biochemistry with a major focus on the application of stem cells and gene therapies for Osteogenesis Imperfecta using animal models. Dr. Niyibizi research continues to focus on bone and stem cell biology and their application in the treatment of musculoskeletal diseases that include osteogenesis imperfecta.

Francis Glorieux
Francis H. Glorieux received his MD from the University of Louvain and his PhD from McGill University. It is there that he developed his interest in heritable pediatric bone diseases. He demonstrated the beneficial effects of bisphosphonate in severe forms of Osteogenesis Imperfecta. Programs based on the Montreal protocols are now used all over the world. He is Emeritus Director of Research at the Shriners Hospital and Emeritus Professor of Surgery, Pediatrics and Human Genetics at McGill. Since 2009, he has been the Chair of the Medical Advisory Council of the Osteogenesis Imperfecta Foundation (USA). He has published over 290 peer-reviewed papers, and co-edited 3 books.
Francois Fassier
Dr. François Fassier completed his medical school in Lyon, France and his orthopaedic residency in Grenoble and Paris. In 1982 he immigrated to Canada and became a member of the Ste Justine Hospital staff until 1993. He was then appointed at McGill University and became Chief of Orthopaedics at the Montreal Children’s Hospital. Director of Pediatric Orthopaedic Surgery at McGill University, he became Chief of Staff of the Shriners Hospital – Canada in 2001 until September 2010. Dr. Fassier introduced the ilizarov method for bone lengthening in Canada and developed a telescopic implant for children with bone fragility (The Fassier-Duval rod for OI). With Dr F. Glorieux he created a Multidisciplinary Clinic for OI patients.

Miguel Galban
In 1993, Dr. Miguel Galbán, after completing a postgraduate course in orthopedics and traumatology at the Central University of Venezuela, entered the Orthopedic Children’s Hospital of Caracas, where he specialized in children’s orthopedics and later was part of the medical staff of that hospital, where he became Medical Director. After conducting a research fellowship in child orthopedics at Alfred I. DuPont Hospital he became a leader in Orthopedics for Children in Venezuela. He is a pioneer in the treatment and correction of both acquired and congenital deformities, rare bone dysplasias, osteogenesis imperfecta, congenital pseudoarthrosis, hypoplastic syndromes and metabolic syndromes with bone involvement. Since November 2014 he has served as president of “SLAOTI” and he currently works in Medellín, Colombia.

Darko Anticevic
Darko Anticevic (MD, PhD) is Professor of Orthopaedic Surgery, University of Zagreb, School of Medicine and senior Consultant at Children’s Hospital, Paediatr. Orthop. Depart. Zagreb, Croatia. President of LOC of 29th Annual EPOS Congress, Zagreb, 2010. and EPOS president (2017/2018). The founding member of Croatian Society for Osteogenesis Imperfecta (1998). President of LOC of 11th International Conference on Osteogenesis Imperfecta in Dubrovnik, 2011. Member of Scientific Committee of 12th I. C. on Osteogenesis Imperfecta Wilmington, DE, USA 2014. 46 publications are indexed (CC, PubMed, Scopus WoS) are cited 134 times and H-index is 6. He is editor/co-editor of two books. He was invited faculty, speaker and/or moderator on more than 50 international Congresses and Courses.

Inger Holm
Inger Holm, Professor, PT, PhD, MHA is working at the research unit, Division of Orthopaedic Surgery, at Oslo University hospital/ Medical Faculty, University of Oslo. Her research fields includes osteoarthritis, physical function, physical activity, motor development/competence in children, outcome measures and patient reported outcome measures (PROM).
Joan Marini
Joan Marini, M.D., Ph.D., is Chief of the Bone and Extracellular Matrix Branch, NICHD. She leads the NICHD Osteogenesis Imperfecta research program, in which clinical and bench research are fully integrated. Her lab generated the Brtl mouse model for type IV OI and has played a leading role in the Consortium for OI mutations. In the last five years, her group has been a leader in the exciting new developments about recessive OI, which have revealed important novel findings on the role of collagen prolyl 3-hydroxylation in bone formation. Her clinical research focuses on children with osteogenesis imperfecta and treatment with bisphosphonates and growth hormone. Dr. Marini received her M.D and Ph.D. in the Medical Scientist Training Program at the Johns Hopkins University School of Medicine. She completed training in pediatrics at Johns Hopkins and Georgetown University Hospital. She did Clinical Genetics specialty training at the NIH InterInstitute Genetics Program. She has twice been awarded the NIH Director’s Award for her work on osteogenesis imperfecta.

Luca Sangiorgi
He is Head of Department of Medical Genetics and Coordinator of Rare Disease Centre at Rizzoli Orthopaedic Institute, Bologna, and Contract professor of Clinical Genetics of Bologna University. He is responsible of 3 National Registers of Rare Diseases (Li-Fraumeni, MHE and OI), a Member of National Coordination Team for Clinical Genetics Department, a Coordinator of many Regional Lab for Bioinformatics and manages the National and Regional Hub and Spoke Network on Skeletal Dysplasia. Contributor of more than 50 articles, he’s an active Member of several international medical associations, serving on the Executive Committee of CTOS as President. He’s currently the clinical lead for the European Reference Network for rare bone diseases (BOND).

Vernon R. Sutton
Dr. Reid Sutton is Professor of Molecular & Human Genetics at Baylor College of Medicine in Houston, Texas. He is attending physician in the Skeletal Dysplasia Clinic at Texas Children’s Hospital where he provides care to children and adults with OI and other skeletal disorders. He is a member of the medical advisory council for the OIF was the Principal Investigator for the OIF Linked Clinical Research Centers, a five-year longitudinal study of OI. He is currently the PI for the Longitudinal Study of the Brittle Bone Diseases Consortium of the Rare Disease Clinical Research Network (BBDC-RDCRN) and the Administrative PI for the BBDC-RDCRN, an NIH-sponsored initiative to advance research in rare diseases.
OTHER CONTRIBUTORS

David Sillence
Professor Sillence is a consultant Clinical Geneticist to the Genetic Bone Clinic at the Westmead hospital and an Emeritus Consultant to the Osteogenesis Imperfecta (OI) clinical service in the Sydney Children’s Hospital based at Westmead. He has served on the Board of OI Australia and the Professional Advisory committees of OI Australia and the OI Federation of Europe. Between 1975-1977 he undertook a population and genetic study of Osteogenesis Imperfecta in Victoria Australia. From this study a new diagnostic and prognostic classification of OI was developed and this has become the foundation of the International Nomenclature of Osteogenesis Imperfecta syndromes.

Tracy Hart
Osteogenesis Imperfecta Foundation (OIF)
Tracy Hart is the CEO of the Osteogenesis Imperfecta Foundation, Inc. (OI Foundation). The Foundation was established in 1970 and is dedicated to helping people cope with the problems associated with OI. The Foundation’s mission is to improve the quality of life for people affected by OI through research to find treatments and a cure, education, awareness, and mutual support. Since 1970, the OI Foundation’s funding for research has doubled every five years, for a total investment of more than $6 million. Funding is available for postdoctoral fellowships to encourage new investigators to begin a career in OI research, and seed grants for preliminary research. All applications are reviewed by the Foundation’s Scientific Review Committee, which includes many preeminent OI researchers and clinicians. Funding also supports the OI Registry and the Linked Clinical Research Centers. See www.oif.org for more information.

Ingunn Westerheim
Osteogenesis Imperfecta Federation Europe (OIFE)
Ingunn Westerheim is the President of Osteogenesis Imperfecta Federation Europe (OIFE). The umbrella organisation was established in 1993 and its members consists of national and sub-national organisation which in one way or another support people living with Osteogenesis Imperfecta (OI). Today the OIFE has 18 European members, being national organisations for OI. Five supporting members are aid organisations and research foundations. Seven associated non-European members are located in Australia, USA, Ecuador, Georgia, Mexico, Peru and Panama. OIFE's mission is to represent their members on a European level, for instance through the umbrella EURORDIS as well as networking between researchers, clinicians, health care providers, organisations and people with OI worldwide. OIFE promotes research and does awareness work in addition to supporting the establishment of OI-organisations in more countries. See www.oife.org for more information.
Abstracts - Invited speakers

LYNDA F. BONEWALD
The Role of the Osteocyte in Muscle/Bone Crosstalk

Lynda F. Bonewald
Indiana Center for Musculoskeletal Health

The close relationship between muscle and bone has long been recognized especially during development where one tissue does not develop in the absence of the other. The mechanical interactions between the two tissues have dominated research under the assumption that the major interaction between the two tissues was the loading/unloading of bone by muscle. We hypothesized that bone and muscle could communicate through secreted factors. We have shown that osteocytes, make factors such as prostaglandin, Wnt3a, and unknown factors that support myogenesis and muscle function. However, with aging, osteocytes produce factors that reduce muscle mass and function. We also have data showing that muscle factors can protect osteocytes against cell death or apoptosis due to glucocorticoids or to reactive oxygen species and that production of these factors are increased with muscle contraction. Several new in vivo studies suggest that bone produces factors that increase and maintain muscle mass in young animals, but that with age, osteocytes actually produce factors that decrease muscle mass and function. It will be important to identify these factors, their specific effect on their target tissue and the effects of aging and exercise in order to develop potential therapeutics.

PAUL COUCKE
Further insights in the pathogenetic mechanism of OI through human and zebrafish

Coucke Paul
Center for Medical Genetics Ghent, Ghent University, Ghent, Belgium

In recent years, also through the advent of next-generation sequencing, our understanding of the clinical and molecular spectrum of Osteogenesis Imperfecta (OI) has dramatically increased with the discovery of many additional genes. Nevertheless, identifying and unifying pathogenetic mechanisms linking different disease genes to the formation of bone fragility remains often a challenge and only limited progress has been made regarding an effective treatment. In the efforts to unravel those mechanisms, the functional characterization of known causal OI genes in patients and animal models is instrumental.

In humans, we focused on specific OI families with apparently unusual clinical characteristics in order to further expand the clinical OI spectrum and the knowledge of the underlying pathways involved in brittle bone disorders. At the other hand we generated and characterized several OI zebrafish models with mutations in col1a1a/b, col1a2, bmp1a, plod2, sp7, fkbp10a/b, tapt1a/b and tmem38b, with the goal to unravel disease pathways through transcriptomic and proteomic analysis and to establish a platform for the future development of therapeutic agents that are beneficial for selective or general patient groups. During the meeting those new developments in human as well as in zebrafish will be presented.
RUUD A. BANK
Molecular insights into lysyl hydroxylation and cross-linking of fibrillar collagens in normal and diseased bone

Ruud A. Bank (1) & Ralph J.B. Sakkers (2). (1) University Medical Center Groningen, Dept. Pathology & Medical Biology, Hanzeplein 1, 9713 GZ Groningen, The Netherlands, R.A.Bank@umcg.nl; (2) University Medical Center Utrecht, Dept. of Orthopaedic Surgery, P.O. Box 85090, 3508 AB Utrecht, The Netherlands.

Formation of mature collagen fibrils out of procollagen α-chains requires a variety of enzymes and chaperones in a complex process spanning both intracellular and extracellular post-translational modifications. Disruption of any of the proteins result in a variety of connective tissue diseases. Lysine (Lys) residues can be modified into hydroxylsine (Hyl) by three lysyl hydroxylases (LH1, 2 and 3). Conversion of the Lys in the telopeptides by LH2 results in the formation of pyridinoline cross-linking. In Bruck syndrome, LH2 is mutated, resulting in a loss of pyridinolines in bone. The same occurs when FKBP65 is mutated; this immunophilin is required for the activity of LH2. In both cases the Hyl in the triple helix are unaffected. In the autosomal dominant forms of osteogenesis imperfecta (OI) an overhydroxylation of Lys in the triple helix (not in the telopeptides) is seen. This is mostly explained by a delayed folding of the mutated (pro)collagen, leaving more time for LH1 and LH3 to modify the triple helix. However, our data also show elevated levels of Hyl in the bone from OI type I, patients that suffer from a haploinsufficiency (and not from a mutation in the procollagen molecule itself). Furthermore, we observed an almost twofold increase in the total amount of glycosylated hydroxylsines in OI type I, III and IV. Interestingly, a recurrent finding reported in OI is a decrease in collagen fibril diameter. The increase in glycosylation observed in the present study is in agreement with the reported decrease in fibril diameter in OI bone, since there is an inverse relation between fibril diameter and the level of overmodification of the collagen triple helix. As the collagen fibril diameter is related to tensile strength of bone, the decrease in fibril diameter is OI is likely to play a role in bone brittleness.

RICA GARVA
Circadian clock regulation of the secretory pathway in fibroblasts
(The clock ticks for collagen)

Richa Garva*, 1, Ching-Yan Chloé Yeung1, Susan H. Taylor1, Adam Pickard1, Ben Claverley1,2, Antony Adamson3, Oliver E. Jenson2, Yin Hui Lu1, David F. Holmes1, Paola Zigrino4, Cornelia Mauch4, Qing Jun Meng**1 and Karl E. Kadler**1

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RG and C-YCY contributed equally.

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Collagen fibrils are permanent structures in the extracellular matrix of connective tissues but the molecular basis for their longevity has not been studied. Here we provide evidence for a chronomatrix that accounts for ~3% of collagen, is replaced daily, and is preferentially susceptible to mechanical damage. We propose that the susceptibility of chronomatrix to damage by cyclic loading protects the permanent collagen during the lifetime of the animal. The chronomatrix is regulated by anti-phasic expression of Sec61a2 and Mmp14. Sec61a2 expression is maximal at night and is essential for procollagen (the precursor of collagen) secretion. Expression of Mmp14 only in the day drives chronomatrix turnover. Rhythmic expression of Mia3 and Pde4d regulates anterograde and retrograde ER-Golgi trafficking of HSP47 (the procollagen chaperone), and provides a regulatory control loop for procollagen secretion. Conditional knockout of Mmp14 in adult mice leads to accumulation of a fibronectin- and collagen-rich chronomatrix resulting in fibrosis. We discuss how loss of circadian control of the matrix can lead to fibrosis and why collagen-rich tissues are predisposed to age-related degeneration.

The research was funded by the Wellcome Trust.

THOMAS WIRTH
Surgery in upper extremities in OI

OI patients need surgical orthopaedic help for two main reasons: fracture treatment and deformity correction. The upper extremity has come more and more in focus, since an increasing number of OI patients have realised that persisting humerus and forearm deformities have a negative impact on their daily activities. This involves impaired dexterity as well as much better strength and usage of the upper extremity i.e. for driving the wheelchair.

Among a collective of around 60 OI patients who are regularly treated in our institution 30 have needed or requested surgical treatment for upper extremity fracture or deformity correction. There is an almost equal distribution of fracture treatment between humerus and forearm. Intramedullary stabilisation is the method of choice, and whenever possible and feasible telescopic rodding is being carried out in the humerus. In the forearm intramedullary K-wire stabilisation using the Morote technique is the common treatment. Those patients (n = 17) who require deformity correction are generally interested in having straightened all three bones of the upper extremity. The majority of patients is severely affected, which makes the surgical intervention a very challenging procedure. The humerus can be stabilised by a Fassier-Duval telescopic nail in most of the cases, using up to three osteotomies. The forearm is more difficult. Several osteotomies are being utilised to straighten out the bones and very thin K-wires (1 to 1.6 mm) inserted for maintaining the position and stability. Only occasionally a cast is required in addition. We like to operate one arm in one session, followed by the contralateral one two to three months later. After healing of the osteotomies and return to full activity the patients appreciate the stability of the arm, a much better pro- and supination which allows them to participate in daily activities with a much better confidence. The complication rate is rather low with only two temporary minor radial nerve
irritations which completely resolved. The telescopic nail revision rate is lowest in the humerus (10%). In the forearm a secondary deformity develops with time in those parts of the bones which are no longer protected according to bone growth. However there is no significant loss of functional skills associated with it.

In conclusion surgical orthopaedic management of the upper extremities is a very rewarding procedure mostly for severely affected OI patients both for fracture and deformity treatment. The functional improvement is significant and lasting and very well appreciated by the patient.

**LARS FOLKESTAD**

Cardiovascular diseases in patients with Osteogenesis Imperfecta – a nationwide, register-based cohort study.


Osteogenesis imperfecta (OI) is a hereditary connective tissue disease often due to mutations in genes coding for type 1 collagen. Collagen type 1 is important in the development of the heart and vasculature. Little is known about the risk of cardiovascular disease (CVD) in OI.

**OBJECTIVE:**
To investigate the risk of symptomatic CVD in OI.

**DESIGN:**
A Danish nationwide, population-based and register-based longitudinal open cohort study.

**PARTICIPANTS:**
All patients registered with the diagnosis of OI from 1977 to 2013 and a reference population matched 5:1 to the OI cohort.

**MEASUREMENTS:**
Sub-hazard ratios (SHR) for mitral and aortic valve regurgitation, atrial fibrillation and flutter, heart failure and vascular aneurisms and dissections comparing the OI cohort to the reference population.

**RESULTS:**
We identified 687 cases with OI (379 women) and included 3435 reference persons (1895 women). The SHR was 6.3 [95% CI: 2.5-15.5] for mitral valve regurgitation, 4.5 [95% CI: 1.4-13.9] for aortic valve regurgitation, 1.7 [95% CI: 1.1-2.8] for atrial fibrillation/flutter, and 2.3 [95% CI: 1.4-3.7] for heart failure. The SHRs were not increased arterial aneurisms or dissections.

**LIMITATION:**
Our results were limited by lacking clinical information about phenotype and genotype of the included patients.

**CONCLUSION:**
We confirm that patients with OI have an increased risk of CVD compared to the general population. This held true even when adjusting for factors that are known to contribute to development of these diseases. Our results suggest that the collagenopathy seen in OI may be part of the pathogenesis of CVD in OI.
Tooth agenesis denotes congenital absence of one or more permanent teeth. Hypodontia is defined as agenesis of fewer than six teeth while oligodontia is congenital absence of six or more permanent teeth, excluding third molars. Population studies on tooth agenesis show a prevalence of 6-8%, of which the majority of the affected individuals will present with one or two congenitally missing teeth, and oligodontia in 0.1-0.2%.

Mutations in the PAX9, MSX1, AXIN2 and EDA genes have been identified in familial oligodontia, and mutations in many other genes have been identified in syndromes in which tooth agenesis is a regular feature. Among syndromes where tooth hypodontia and oligodontia is a regular feature are ectodermal dysplasia (ED), Down syndrome and Williams syndrome. Oligodontia was reported in 0.9% in a Swedish population. Most of these individuals were clinically and radiographically diagnosed having ectodermal dysplasia (ED), and none had osteogenesis imperfecta (OI).

Tooth agenesis has been found to occur in up to 22% in patients with OI. In a recent study tooth agenesis was found in 17% (hypodontia 11%, oligodontia 6%) and was more frequent in those with DGI. It was found that collagen I mutations were associated with oligodontia, and that missing teeth is a feature associated with qualitative collagen type I mutations. The high prevalence of tooth agenesis highlights the importance of dental radiographic examination in early school age for short and long term treatment planning. Decision on maintenance or extraction of primary teeth without permanent successors must be evaluated. The growth pattern of the jaws is often complicated in individuals with OI and treatment planning must involve specialists within pedodontics, oral surgery and orthodontics.

HOLLIS CHANEY
Pulmonary Complications of Osteogenesis Imperfecta

The most common cause of death in Osteogenesis Imperfecta is from respiratory failure. The chest wall and lungs are both affected by OI, leading to progressive respiratory complications and symptoms. This talk is to discuss what goes wrong in the pulmonary system is someone with OI, to discuss pertinent research, and to discuss various methods of treatment.

NADJA-FRATZL-ZELMAN
Bone material characteristics in human Osteogenesis imperfecta (OI) and mouse models

Nadja Fratzl-Zelman, Ludwig Boltzmann Institute of Osteology at Hanusch Hospital of WGKK, Vienna, Austria and AUVA Trauma Centre Meidling, 1st Med. Dept., Hanusch Hospital Vienna, Austria;

Bone is optimized to resist fractures by a multiscale structural organization based on a nanocomposite consisting of 2-4 nm thick carbonated hydroxyapatite platelets embedded within type I
collagen fibrils. Its fragility in OI arises not only from reduced bone mass but also from altered material properties.

Transiliac biopsy samples and murine bones, originally prepared for histomorphometry, were investigated by quantitative backscattered electron imaging, small-angle X-ray scattering and Raman micro-spectroscopy to determine the Bone Mineralization Density Distribution as well as the characteristics of mineral and matrix consisting of collagen, non-collagenous proteins and water.

The major finding is a hypermineralized matrix in OI, independently of the underlying mutation type or clinical severity. Despite the elevated calcium content, mineral particle size was found smaller or equal than in healthy bone. This indicates a higher packing density of mineral particles within the matrix and correlates with a reduced water content of collagen. The increased mineral content likely affects bone material quality, making it stiffer than normal and prone to fractures.

Recently, it was shown that the osteoblast-derived proteins BRIL and PEDF each influence the other’s expression level. Mutations in their respective genes cause OI type V, type VI and atypical type VI with striking mineralization abnormalities. Type V lacks proper bone lamellation and elevated osteocyte lacunar density in addition to the hypermineralized matrix, which suggests exuberant primary bone formation. Type VI and atypical type VI show both very highly mineralized matrix coexisting with poorly and unmimeralized bone areas and disordered fibril organization in the perilacunar regions of young osteocytes. Furthermore, the presence of chondrocytes in abnormal differentiation states suggests a singular endochondral ossification defect in atypical type VI.

As highlighted by these studies, bone material is an essential phenotypic characteristic of OI without which the pathophysiology of the disorder cannot be fully understood.

CHRISTOPHER NIYBIZI
Animal models of osteogenesis imperfecta and their application in testing novel therapies

Christopher Niyibizi, PhD.
Penn State College of Medicine, Hershey PA, USA 17033

A number of animal models for osteogenesis imperfecta have been identified. Most of the animal models are transgenic mice created to mimic specific OI phenotypes to understand how mutations observed in humans cause the disease. Close to 20 animal models of OI have been described to date but their application to test novel therapeutic drugs or stem and gene therapies are limited. There are few animal models with naturally occurring mutations in the genes that encode bone related proteins that cause OI; in addition, there is limited number of large animals with OI to evaluate various treatments. Transgenic mice are expensive to maintain and some of them do not breed well and thus only few animals are available to carry out experiments to test novel drugs or stem cell and gene therapies. We will discuss animal models of OI available and some of the preclinical work that has been done in testing various therapeutic options and problems associated in applying some of these animal models. A mouse model of OI called oim, lacks expression of type I collagen alpha 2 chains and has been used extensively to test various treatments for OI. The mouse has a naturally occurring mutation in collagen alpha 2 chain, it is easy to generate several homozygous mice by...
breeding heterozygous mice and therefore this mouse model has become the choice for investigators evaluating various treatments for OI specifically cell therapies. This mouse model however, does not represent the typical OI phenotypes in which a conserved glycine in every third position in collagen alpha chains occurs, thus its use is limited. Studies that we and other have done using this mouse model to evaluate stem cell therapies for OI will be discussed as well as obstacle to be overcome.

**BRENDAN LEE**

**Implications of Excessive TGFβ signaling in Collagen-related forms of OI on Treatment**

Brendan Lee, MD, PhD Department of Molecular and Human Genetics, Baylor College of Medicine, Houston TX, USA

Structural mutations in type I collagen and defects in the prolyl-3-hydroxylation lead to collagen post-translational over-modification and increased TGFβ signaling both in vivo and in vitro. Importantly, blockage of TGFβ using a pan-anti-TGFβ antibody shows significant rescue of the bone bone phenotype in OI mouse models. A human version of this antibody is now currently being tested in phase I clinical trials by the Brittle Bone Disorders Consortium of the National Institutes of Health Rare Diseases Clinical Research Network (RDCRN). Importantly, the validation of increased TGFβ signaling has broader implication on the therapeutic approaches to treating OI including the effects of teriparatide in the adult population.

**JOAN C. MARINI**

**What is Osteogenesis Imperfecta (OI) in 2017?**

Joan C. Marini, MD, PhD (invited talk)

**Background:**
The last decade has seen developments in (a) OI genetics with the identification of 14 new genes for dominant, recessive (mostly) or X-linked OI, (b) information about bone tissue in OI, and (c) understanding of OI pathophysiology from murine and patient samples. It is now appropriate to consider the common elements that define OI across the types.

**Methods:**
Compilation of reports in literature on the genetics, mechanism and bone tissue of OI in patients and animal models.

**Results:**
The OI genes delineated in the last decade largely encode proteins that interact with collagen for folding, modification, and/or cross-linking. Other genes affect bone mineralization or osteoblast maturation. Several combinations of OI gene products interact with each other directly or in interactive pathways: CRTAP/P3H1/CyPB, BRIL/PEDF, HSP47/FKBP65, and OASIS/S2P. Some serve as foldases for collagen or collagen modifying proteins: *e.g.* CyPB for the collagen helix and LH1, FKBP65 for LH2. The biochemical consequences of type I collagen structural or interactive
abnormalities encompass abnormal chain alignment and incorporation, slow folding and over- or under-modification, ER retention, reduced secretion and matrix incorporation. Bone from many OI types is weak, brittle, and hypermineralized; it has an abnormal pattern of collagen crosslinks, and a high turnover cellular pattern. In addition, osteoblasts and osteocytes from some OI types have impaired differentiation and chronic ER stress. OI matrix displays collagen insufficiency in many types.

Conclusions:
Osteogenesis imperfect is a collagen-related disorder caused by an array of genes with functionally interacting protein products. This talk presents a current integration of common features of known OI types. Continued investigations on samples from patients and animal models is needed to fully understand the network of interactions of these proteins and the common molecular/cellular pathways of OI. Ultimately, this knowledge is likely to lead to insights underlying new therapeutic approaches.

**DAVID SILLENCE**
**Nosology and Classification of Osteogenesis Imperfecta**
**230 Years of Discovering Genetic Heterogeneity**

David Sillence, MD, PhD, Sydney, Australia (introduction)

Genetic heterogeneity in the heritable disorders of bone fragility (osteoporosis and fractures) has been well established for over 40 years. When Olaus Ekman presented his doctorate on “A fragile boned family” in 1788, there was no mention of blue sclerae. When families were described with autosomal dominant inheritance of bone fragility and distinctly blue sclerae, debate started about whether there was a single disorder or multiple disorders with bone fragility. In 2015, the International Nosology Committee for Constitutional Disorders of the skeleton recognized five groups of disorders (previously OI types I – V) which are now known by a characteristic phenotypic name or by Arabic Numerals as OI types 1-5. Studies firstly with connective tissue proteins, then molecular genetics and more recently genomics show that these 5 phenotypes and special syndromes with phenotypic features overlapping OI, are due to mutations in at least 24 distinct gene loci. Three patterns of inheritance (autosomal dominant, autosomal recessive and X-Linked recessive) have been observed. All of the phenotypic groups apart from OI type 5 show considerable genetic heterogeneity. Several more genes in which mutations result in a brittle bone disorder are being investigated. The serial numbering of mutant gene loci in OMIM (now up to OI type XVI) does not address the concerns of predicting a phenotype. On the other hand the simplicity of a phenomic description of the OI syndromes does not detract from the uniqueness of the mutations in these many distinct loci being investigated at the research level.

Genomic and functional studies in the last 5 years have given even more insight into the pathogenic mechanisms responsible for bone fragility. In particular GWAS studies (Rivadeneira and Makitie 2016) suggest that there are many more loci which have a quantitative trait locus (QTL) modifying effect on bone density or on fracture liability. There is no inconsistency between major locus segregation (eg an X-Linked recessive form of OI resulting from mutation in PLS3) and the separate description for the gene PLS3 as a QTL.
Abstracts - Oral Communications

O1
Growth Characteristics in Osteogenesis Imperfecta – Results from an Observational Study from the Linked Clinical Research Centers and the Brittle Bone Disorders Consortium
Vernon Reid Sutton, Professor
Houston, United States of America

Osteogenesis imperfecta (OI) predisposes to recurrent fractures and bone deformities, which affect growth. There are few large-scale studies that have systematically investigated growth in OI. The Linked Clinical Research Centers (LCRC), a network five clinical centers across North America was established to advance research and patient care in OI. From the LCRC data, we compared height, weight, BMI and arm-span to height ratio in 553 individuals with OI (types I n=244; III n=110; IV n=150; V n=16; VI n=12; VII n=5; unclassified n=16). In the pediatric population (age < 20 years), the median (IQT) Z-scores for height in OI types I, III, and IV were -0.66(-1.43,0.02), -6.91(-8.41,-5.17) and -2.79 (-3.95,-1.69), respectively. In severe forms of OI, we observed significantly diminished growth velocity. Although the median Z-score for weight in children with OI type III was 4.55, the odds of them being classified as overweight and were 2.48 and 5.23, respectively, as compared to OI type I. The median (IQT) of Z-scores for BMI in the pediatric population in OI types I, III and IV were 0.10(-0.58-0.94), 0.91 (0.42-1.61) and 0.67 (-0.18-1.33). Thus, the standard method for calculation of BMI in the general population may not be accurate in OI. The arm-span/height was significantly different in adults with OI types III and IV, as compared to OI type I, and thus demonstrates axial and lower limb growth restriction/deformation compared to the upper extremities. Generalized linear model analyses demonstrated that reduced height Z-score positively correlates with severity of OI subtype (p<0.001), age, bisphosphonate use and rodding (p<0.05). This cross-sectional analysis of the largest cohort of individuals with OI, provides median values for growth parameters which can aid as a reference during clinical evaluation. Through the Brittle Bone Disorders Consortium, we plan collect longitudinal data and develop standardized growth curves specific to OI.

O2
Longitudinal Growth Curves for OI Caused by Structural Mutations in Type I Collagen
Joan Marini, Senior Investigator
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Objective:
Growth deficiency is a cardinal feature of OI caused by collagen structural mutations, which in practice refers to Types III and IV OI. Growth deficiency is generally marked by the first year of life and progresses thereafter. OI-specific longitudinal growth charts are needed to guide caregivers and families.

Methods:
From 100 participants in the NICHD/NIH longitudinal research program on OI, we compiled length, weight and head circumference from ages 2-17. Of the total, 55 are females, 56 have type IV OI and 56 have mutations in COL1A1. Data was binned into half year intervals and was analyzed by gender, type and mutated gene using nonlinear multilevel modeling (SPSS) with percentile curves constructed using the GAMLSS package from R.

Results:
Sex and OI type had significant effects on stature and weight while the specific collagen gene causing the OI did not. The effect of OI type was greater than that of gender. Interestingly, head circumference was not significantly different by gender, type or mutated gene. OI-specific standard curves for height and weight were
generated by gender and type. When OI height curves are superimposed on USA CDC growth curves, types III and IV curves overlap in both girls and boys, with the type III 50th centile curve similar to the type IV 5th centile in both genders. In girls, the type III 95th centile curve exceeded the type IV 50th centile curve, while the reverse occurs in boys. In both genders, the type IV 95th centile curve overlaps the lower general population curves. A pubertal growth spurt is generally not seen in type III OI, and is blunted in type IV.

Conclusions:
OI type is a stronger discriminating factor than gender for OI growth, while curves do not differ for COL1A1 vs COL1A2 mutations. OI-specific growth curves will facilitate care.

O3
A familial FKBP10 mutation associated with a wide phenotypic spectrum ranging from Arthrogryposis to OI.
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Objectives
Recessive mutations in the FKBP10 gene result in Osteogenesis Imperfecta (OI) or Bruck Syndrome (BS) where bone fractures are accompanied with contractures. In addition, a specific homozygous FKBP10 mutation (p.Tyr293del) has been described in Yup’ik Eskimos to cause Kuskokwim syndrome (KS) in which contractures without fractures are observed. Here we present an extended Palestinian family with 10 affected individuals in which the three above mentioned syndromes segregate.

Patients and Methods
DNA was extracted from an EDTA-blood sample of 10 affected family members (ranging from 6 – 47 years) of a Palestinian consanguineous family of whom two patients have only fractures (n > 50), seven patients have fractures (n > 20) and contractures and one patient has only contractures mainly in the lower limbs and no fractures, clinically diagnosed as arthrogryposis. The coding region and flanking introns of all known recessive OI genes were sequenced using NGS. A fibroblast cell culture from the proband was established and RNA was purified to synthesize cDNA.

Results
A novel homozygous splice site mutation, c.391+4A>T in intron 2 of the FKBP10 gene was identified in the proband, causing skipping of exon 2 (p.Tyr83Glyfs*66) and absence of the FKBP10 protein. Segregation analysis revealed that all 10 patients harbor this homozygous splice site mutation whereas non-affected family members are either heterozygous carriers or non-carriers. Additional clinical features are progressive scoliosis (9/10), blue sclerae (6/10), dentinogenesis imperfecta (4/10), club foot (4/10) and hernia (2/10).

Conclusion and take home message
Our findings illustrate that single familial FKBP10 mutations can result in a phenotypic spectrum, ranging from fractures without contractures, to fractures and contractures and even to only contractures. This broad intrafamilial clinical variability within one single family is a new finding in the field of bone fragility.

Disclosure statement:
The authors declare no commercial financial support for this work.

O4
Use of patient-specific iPSCs as a platform for genotype-phenotype analysis of OI
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Cultured fibroblasts from subjects with OI or murine models of OI have provided major insights into the cell and molecular basis of this extremely heterogeneous disorder. However these models do not account for the background genetic factors that influence disease severity or can distinguish the cell autonomous and non-cell autonomous effect of the underlying gene mutation.

Objective:
Present a method for generating a human organoid of osseous and cartilage tissue from iPSCs in vivo within a mouse calvarial defect.

Method:
iPSCs were generated using a non-integrating vector delivery system, were inducted to form embryo bodies (EBs) that were subsequently expanded in an endothelial growth factor medium. Upon implantation of these cells in the NSG mouse, a mound of tissue forms that begins to produce mineralized cartilage by 6 weeks and island of osseous tissue by 10 weeks. The organoid is analyzed using a non-decalcified cryohistological procedure optimized to discriminate human and mouse tissue.

Results:
A subject with type III/IV OI failed to make these tissues and instead produce adipocytic tissue. Upon CRISPR/CAS correction of the mutation, the expected cartilage/osseous tissue was generated. Subjects with type I and type IV OI make the expected organoid of varying size and show no obvious histological abnormality. In all cases, the organoid is not modified by the mouse hematopoietic/osteoclastic cells, providing the opportunity to assess the cell autonomous impact of the mutation. Currently we are developing methods to extract, amplify and analyze RNA from specific tissue regions of the formed tissue using laser capture microdissection, and to engineer the iPSCs to be recognized and modified by the mouse hematopoietic system so that the non-cell autonomous effects of the mutation can be assessed.

Take home:
With continued technological advances, this platform could have diagnostic and therapeutic applications that are tailored to a specific individual with OI.

O5
SPARC-related osteogenesis imperfecta with a myopathy-like presentation
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We report two sisters with healthy consanguineous parents, normal birth measurements, pes adductus, persistent hypotonia, small joint laxity, delayed motor development and progressive early thoracolumbar scoliosis. Pathological fractures started at age two years and loss of primary dentition was delayed. Molecular testing did not confirm the initial suspicion of Ullrich congenital muscular dystrophy.

Multiple fractures and low bone mineral density led to molecular testing for osteogenesis imperfecta (OI). Exome sequencing showed no coverage of exon 4 in SPARC in either girl. Deletion breakpoints were determined by Sanger sequencing. The homozygous variant c.121-578_209-94del (NM_003118.3) present in both children introduces a change in reading frame likely resulting in nonsense-mediated decay.

Mendoza-Londono et al (1) demonstrated biallelic loss-of-function mutations in SPARC in two unrelated girls with severe bone fragility, progressive scoliosis and joint hyperlaxity. Ullrich muscular dystrophy was initially suspected in one. Subsequently, two siblings with marked joint laxity, progressive scoliosis and short stature with
a homozygous splice site variant in SPARC were reported (2).

We describe the oldest known individual with SPARC-related OI and further delineate the phenotype. The resemblance to a congenital muscle disorder prior to the onset of fractures is in keeping with evidence that SPARC (secreted protein acidic and rich in cysteine) interacts with actin in muscle cells during development and remodeling (3).


O6
Biochemical characterization of a COL1A1 signal peptide heterozygous mutation leading to severe OI
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The most frequent genetic cause of OI are deleterious variants in the genes encoding type I collagen (COL1A1 and COL1A2), which build the organic scaffold of the bone matrix. These mutations are thought to cause quantitative and/or qualitative defects of bone collagen and may lead to a wide range of clinical presentations, from mild to lethal. Type I collagen is a heterotrimer consisting of two α1(I) and one α2(I) chains that fold in the rough-endoplasmic reticulum (rER) to form a triple helix of uninterrupted Gly-X-Y repeats, followed by secretion into the extracellular space via the trans-Golgi network.

A rare heterozygous p.Gly22Arg disease variant at the the -1 position of the signal peptide cleavage site of COL1A1 was identified in a foetus presenting at ultrasound examination with bowing and shortening of all long bones and a diagnosis of severe OI. The signal peptide is required for the translocation of the nascent collagen α-chains to the ER and is subsequently cleaved off by a signal peptidase. We set out to characterize the p.Gly22Arg mutation at the biochemical level, in order to gain insights into the pathomechanism leading to OI. Production of procollagen I was reduced and secretion was slightly delayed. Furthermore, aberrant procollagen α1(I) and α2(I) chains were detected in the cell layer by pulse-chase analysis, suggesting the presence of both overmodified, as well as undermodified collagen chains. In vitro, ultrastructural analysis of cultured fibroblasts showed the presence of enlarged ER-cisterns. Immunofluorescent staining, aimed to test for accumulation of aberrant procollagen I chains in the ER, showed a punctuate staining that did not overlap with either ER- or Golgi markers. Taken together, our data point towards the intracellular retention of aberrantly folded procollagen I and possibly the involvement of ER-stress as pathomechanism leading to OI in the affected foetus.

O7
Chemical chaperone treatment ameliorates cellular homeostasis of patients with Osteogenesis Imperfecta
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Objectives.
The molecular basis of classical forms of osteogenesis imperfecta (OI) is attributed to the presence of an abnormal extracellular matrix and to the impairment of its structural integrity. Here
we propose that the OI cell homeostasis may be significantly affected by cellular stress and malfunction caused by the retention of mutant collagen and thus that cellular response to collagen retention, together with the altered matrix, is a key component in OI pathogenesis.

Methods. The cellular response was investigated in patients fibroblasts with mutations both in collagen type I α1 and α2 chains by western blot analyses, immunohistochemistry, cytofluorimetry and electron microscopy.

Results.
We detected an intracellular retention of the aberrant protein, the presence of an endoplasmic reticulum (ER) enlargement and the activation of the unfolded protein response (UPR).

Patients cells with collagen type I α1 mutations respond to the mutant collagen retention by activating autophagy as demonstrated by the increase of the terminal autophagic marker LC3II. Autophagy is instead not always activated in cells with collagen type I α2 mutations. Even if the cell is reacting to the stress some degree of apoptosis occurs, as demonstrated by the increased level of the terminal cleaved caspase 3. To reduce stress, cells were treated with the FDA-approved chemical chaperone 4-phenylbutyric acid (4-PBA). The drug decreased the activation of the UPR stress sensor and reduced cell apoptosis.

Conclusions.
Cellular stress caused by the presence of mutant collagen type I molecules is a key component in OI pathogenesis and cellular response to ER stress can be an important modifier of disease severity.

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O8
Incidence and treatment of femur fractures in adults with Osteogenesis Imperfecta
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Objectives
Osteogenesis Imperfecta (OI) is known for increased bone fragility and susceptibility for fractures. A few studies compared treatment modalities of femur fractures in children having OI. However, large studies in adults are lacking. This large cohort study of adult OI patients aims to give an insight into the incidence of femur fractures and its best treatment to avert non-union.

Methods
All patients of 16 years or older known in the OI expert clinic in the Netherlands were analyzed retrospectively. Information on type of fracture and fracture treatment, smoking status, bisphosphonate use, number of fractures during lifetime, femoral and/or lumbar spine bone mineral density and demographic characteristics were collected.

Results
In 224 OI patients, 34 patients suffered a femur fracture with 11 having more than 1 femur fracture. In 50 total fractures, 10 resulted in a non-union with most being midshaft fractures in type IV OI patients. Having over 36 fractures during lifetime was associated with a higher non-union rate. Operatively treated midshaft fractures gave best results for non-union outcome.

Conclusion and take home message
This is the first cohort study on femur fractures in adult OI patients giving an overview on fracture and non-union incidence and its treatment. Although a large cohort of subjects is included, an even larger study is needed to distinguish between intramedullary nailing and plate fixation. A humeral nail could offer a good solution challenging the narrow intramedullary canal in patients with OI.
Challenges of treating the tibia in patients with osteogenesis imperfecta. A single surgeon series

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Objectives:
To present our experience in treating tibial deformity in osteogenesis imperfecta (OI) and address its specificities.

Methods:
We report on OI patients with multiple long bone deformities treated at our Department in the period from July 1986 to July 2015. All patients had corrective osteotomies of the tibias performed, followed by various methods of fixation.

Results:
There were 13 patients (5 female, 8 male), with 46 surgeries [median 2.5 per patient (range, 1-10 surgeries per patient)] performed on the tibia. Median patient age at time of surgery was 7 years (range, 2-12 years). Methods of fixation were as follows; 2 DC plates, 2 Rush nails, 16 IM K-wires, 7 IM Nancy elastic nails and 11 IM Fassier-Duval nails. Median follow-up was 10.5 years (range, 3-36 years). A number of complications were noted, mainly protrusion of the IM implant proximally, in the knee, or distally, in the ankle joint (5 patients). One patient had a protrusion of the telescopic nail through the anterior tibial cortex. Two patients suffered a refracture with the IM fixation in place.

Conclusions:
Surgical treatment of tibial deformity in OI patients by means of IM rodding is burdened with high recurrence of deformity due to poor bone quality, and complications inherent to the used hardware. However, successful correction and maintenance of the bone axis gives patients a chance of growth and better ambulation, which is why all our patients agreed to multiple corrective surgeries even after knowing the rate of complications beforehand.

Take Home message:
Tibia is the ‘problem bone’ for surgical treatment in OI patients, mostly due to its triangular shape, narrow diameter, smaller distal physis, deformed adjacent fibula and the gastrosoleus complex. The third-gen telescopic nails that allow for growth while maintaining correction are currently the state-of-art technique.

Results of combined intramedullary nailing and supplemental fixation of long bones in patients with osteogenesis imperfecta (OI)

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Objectives:
For children with OI intramedullary rodding of the long bones has been established as standard of surgical fixation for fractures, corrective osteotomies and treatment of nonunion. Since the introduction of bisphosphonates different efforts were made to find supplemental fixation methods, which can solve the remaining problems and decrease the risks of intramedullary fixation alone. The aim of our study was to describe the technique and results of additional plate, staple ore screw fixation in OI-Patients of a single center population.

Method:
This is a retrospective study of 26 patients with OI, who have undergone intramedullary fixation as well as supplemental fixation at osteotomy or fracture sites and nonunion. We evaluated clinical status, functional and radiological course.

Results:
We present our preliminary results of combined fixation strategies in OI-Patients. A total number of 31 long bones were treated with intramedullary and supplemental devices (18 femora, 10 tibiae, 2 humeral and 1 radial bone. Intramedullary devices
included telescoping and non elongating systems. The mean follow-up time was 12 months. 30 long bone segments have shown stable healing. The average time to union was 8 weeks (6.5-18 weeks). In 28 of the long bone segments, the supplemental fixation was applied at fracture or osteotomy level. In 3 cases, supplemental plate fixation was applied to the site of a nonunion.

Conclusion:
Supplemental fixation provides a valuable option to improve the status in this severely affected patient population. Further follow-up is necessary to improve our knowledge about the long term outcome.

Take home message:
With the help of additional fixation devices we can avoid longer cast fixation, achieve rotational stability and earlier weight bearing.

Disclosure:
There is no financial support from commercial parties.

O11
Management of the Upper Extremity in OI: 20+ years’ experience
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Objective
Upper extremity (UE) surgery in OI represents only 10% of all surgeries done for these patients. This may be due to the belief that UE problems are primarily cosmetic, the difficult surgical approach required for UE bones, the lack of outcome studies demonstrating the effect of rodding surgery, and possibly the lack of interest of surgeons in UE problems. Our goal (which follows the presentation on UE assessment) is to provide guidelines on surgical decision making. Topics to be addressed include indications for surgery, technical aspects of surgeries, associated complications and non-surgical options.

Methods
A retrospective chart review was conducted on 54 children who underwent UE rodding at our institution between 1994 and 2013. Information on function, technical aspects (antegrade versus retrograde humeral rodding), and specific outcomes (pseudoarthrosis of the distal humerus, elbow in OI type V) was collected.

Results
Osteotomy and rodding of the humerus and/or forearm bones are indicated if non-surgical options (i.e. modifications of medical treatment for recurrent fractures) have proven to be insufficient, or if severe bony deformities limit function (see previous communication). Functional gains from forearm rodding were greater in moderate OI than in severe OI. Functional gains from humeral rodding were greater in the self-care domain than mobility domain with reports of increased confidence in the UE. Angular deformity improved in all patients undergoing UE rodding. Complications included non-union and prominent hardware. The early results of a simple approach for humeral rodding (retrograde without going through the rotator cuff) are encouraging.

Conclusion
Surgery yields positive gains however the relationship between UE deformity (which is not only a cosmetic issue) and function in OI is still not clearly defined.

Take home message
Surgical management of UE deformities is offered after a comprehensive evaluation (including function) by the OI team.

Disclosure:
Royalties received from PegaMedical

O12
Treatment of Scoliosis in Osteogenesis Imperfecta with Cement-augmented Pedicle Screw Instrumentation: A Preliminary Experience in Single Institute
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Objectives:
Spinal surgery in Osteogenesis Imperfecta (OI) historically has been fraught with complications and many patients are counseled against surgery. Our aim was to investigate if pedicle screw fixation with/without cement augmentation provide spinal stabilization with fewer complications and improve clinical outcomes in OI with scoliosis.

Methods:
Patients from a single institution who underwent posterior only scoliosis surgery between 2005-2017 were reviewed retrospectively. Patients with minimum one year follow-up were included. Preoperative and postoperative ambulatory status and clinical outcomes were evaluated. Surgical and radiographic data were recorded. Radiographic review included: pelvic obliquity, major curve magnitude (Cobb angle), deviation in coronal balance, apical vertebral translation (AVT), lowest instrumented vertebrae (LIV) tilt angle, proximal and distal junctional angle, T1-S1 distance and T1-Pelvic angle (TPA). Non-parametric Friedman test was used for comparison among radiographic data.

Results:
Fourteen patients met inclusion criteria. The average follow-up was 44±29 months (range,14–110). The median preoperative Cobb angle 81° (55-114°) was significantly higher than both, first 21(12-39°) and last 21 (14-24°) postoperative Cobb angle (59% correction; P<0.001). No correction loss was found during the follow-up. The median preoperative AVT and LIV tilt angle were significantly higher than both, first and last postoperative measurements (P<0.001 and P=0.002, respectively). There was no significant difference in coronal balance, pelvic obliquity and T1-S1 distance among the preoperative and the first and last postoperative measurements (P=0.479, P=0.096, P=0.05, respectively). No patient underwent revision surgery due to proximal junctional failure. One distal junctional failure was treated with cement-augmented pedicle screw fixation. Ambulatory status remained unchanged in all patients, clinical and functional improvement was observed.

Conclusion:
Pedicle instrumentation system with/without cement augmentation provided increased stability with few complications in patients with OI and scoliosis.

Take home message:
The scoliosis surgery did not change ambulatory status, but resulted in postoperative clinical and functional improvement.

O13
Acetabular Protrusio in Osteogenesis Imperfecta: Progression and Risk Factors
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OBJECTIVES
The purpose of this study was to (1) characterize the development of acetabular protrusio over time in patients with osteogenesis imperfecta (OI) and (2) identify patient risk factors associated with development of acetabular protrusio in the context of OI.

METHODS
Medical records and radiographs of 55 patients (109 hips) diagnosed with OI were retrospectively reviewed. Using anteroposterior pelvic radiographs taken at least 2 years apart, acetabular protrusio was determined through previously established radiographic criteria: center-edge (CE) angle of Wiberg, position of the acetabulum relative to the iliopectineal line, crossing of the acetabulum across the ilioschial line, and position of the teardrop figure relative to the ilioschial line.
RESULT
Acetabular protrusio was observed in 45% (49 out of 109 hips) and 66% (72 out of 109 hips) of hips in the first and last radiographs, respectively. Twenty-four out of 49 hips that did not initially meet criteria for protrusio (40%) met criteria by the last evaluated radiograph. There was a significant increase in CE angle and ilioischial line crossing by the acetabulum over time (p < 0.005). Patient factors associated with increased risk for development of protrusio included (1) an age under 12, (2) a BMI greater than 25, and (3) female sex. Therapeutic interventions such as bisphosphonates, vitamin D, and physical therapy did not significantly reduce risk of protrusio development.

CONCLUSION
The present study demonstrates that protrusio-related radiographic measurements (CE angle and ilioischial line) change significantly over time in patients with OI. In our study, 40% of hips that did not initially meet criteria of acetabular protrusio on the initial radiograph eventually met the criteria after a period of at least 2 years.

TAKE HOME MESSAGE
Acetabular protrusio is not a static condition and develops over time in patients with OI.

O14
Prevalence and progression of spondylolisthesis in children with Osteogenesis Imperfecta.
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Objectives:
To determine the effect of disease characteristics and medical management on the presentation and progression of spondylolistheses in children with Osteogenesis Imperfecta (OI).

Methods:
A retrospective chart audit was conducted of children with OI attending a tertiary centre between 2005 and 2015. The presence or absence of spondylolisthesis was measured on lateral x-rays as a percentage slip, then graded one through four using the The Meyerding Classification system. Demographic and medical information including presence or absence of scoliosis, basilar invagination, hypermobility, type of bisphosphonate used and age commenced, were collected from patient records.

Results:
Records of one hundred and forty children were reviewed with a mean follow-up period of 6.8 years (SD 4.38 years). Prevalence of spondylolisthesis was 42.9% overall. Spondylolistheses were significantly more prevalent, initially presenting at a younger age and with a higher maximum slip percentage in children with Type III (91%, mean 2.02 years, mean 40% slip), than Type IV (50%, mean 7.8 years, mean 12% slip) and Type I (32%, mean 6.01 years, mean 8% slip) (all p < 0.001). Characteristics suggestive of a more severe phenotype were significantly more prevalent in children with a spondylolisthesis (basilar invagination 10%, scoliosis 25%, dentinogenesis imperfecta 41%) than without (basilar invagination 1%, scoliosis 11%, dentinogenesis imperfecta 10%) (all p <0.001). The grade of spondylolisthesis remained stable throughout follow-up in 70% of children with 17% progressing, 6% regressing and 7% fluctuating over time. There were no significant differences in the disease characteristics between children whose spondylolisthesis remained stable or progressed.

Conclusion:
Spondylolistheses present early and are prevalent in children with OI, particularly in more severe disease types.
Take-home message:
Clinicians working with children with OI should monitor for spondylolisthesis from a very young age, particularly in children with more severe phenotypes. Prospective longitudinal studies are needed.

O15
Scoliosis and Cardiopulmonary Outcomes in Osteogenesis Imperfecta
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PURPOSE:
OI has been distinguished as a disorder of connective tissue, which can result in respiratory insufficiency—the leading cause of death in OI patients (McAllion, 1996). Correlations between scoliosis and decreased pulmonary function have been shown (Falvo, 1974; Wekre, 2014). However, it has been suggested that decreased pulmonary function may be an intrinsic component of OI, rather than a secondary effect of scoliosis (Widmann, 1999). We hypothesized that reduction in pulmonary function is intrinsic to OI, rather than scoliosis.

METHODS:
176 OI patient records were retrospectively reviewed. Anteroposterior radiographs were evaluated for scoliosis (curve >10°). If more than one curve was present, the largest curve was used for analysis. Pulmonary function was defined by FEV1/FVC ratio. Bivariate correlation analysis was performed, using Spearman’s rho correlation coefficient.

RESULTS:
57.2% of patients were female (ages 25-84). 43.4% of patients had OI Type I, 17.0% Type III, 23.3% Type IV, 1.3% Type V, 1.3% Type VIII, 1.3% Type IX, and 12.6% were unclassified. 18.9% of patient charts included radiographs and PFTs. 21.4% of patients had pulmonary comorbidity, while 18.9% had cardiac comorbidity present. Correlation between scoliosis and pulmonary function was weak (R=0.059) and not statistically significant (p=0.747).

CONCLUSIONS:
Pulmonary function (FEV/FVC) is weakly correlated with scoliosis. Therefore, decreased pulmonary function is most likely an intrinsic factor of OI, rather than scoliosis. Although respiratory insufficiency is known to be the leading cause of death in OI patients and regular PFTs are suggested as standard-of-care, most patients did not have PFTs done. This illustrates the need for greater emphasis on the importance of cardiopulmonary health and annual PFTs.

SIGNIFICANCE:
We stress the medical importance of annual lung functions to better elucidate the underlying cause of cardiopulmonary insufficiency and minimize morbidity and mortality.

O16
Dental occlusion and temporomandibular disorders in adults with osteogenesis imperfecta
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Osteogenesis imperfecta (OI) is a rare inherited disease characterized by fragile bones because of defective collagen synthesis. OI can be divided into mild OI (Silence type I) and moderate-severe OI (Silence type III-IV). The dental and skeletal aberrations of OI might influence the temporomandibular function.
The aims of study were to assess the dental occlusion and the occurrence of temporomandibular disorders (TMD) in adults with OI and to carry out a comparison of occlusal traits and TMD according to severity of OI.

All participants (n = 75) had mutation in COL1A, and they were classified with mild OI (n = 56) or moderate-severe OI (n = 19). Dental occlusion was assessed on clinical photos and 3D models. The participants were examined according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD).

Results.
Mandibular overjet and posterior cross-bite were more prevalent in moderate-severe than in mild OI group (P < 0.050). Temporomandibular disorders and functional limitations in the orofacial region were rare and did not differ between patients with mild and moderate-severe OI (P > 0.050). Myofascial pain was rare in both groups. Disc displacement and other joint diagnosis were rare and difference in the occurrence between groups was minimal. Reduced jaw opening was more prevalent in moderate-severe than in mild OI (P = 0.037). No significant differences between Graded Chronic Pain Scale grades 0, 1, and 2 were found in mild OI vs. moderate-severe OI (P > 0.160). Few patients (16%) had signs of depression, but close to half (48%) had signs of somatization.

Conclusion.
Mandibular overjet and posterior cross-bite were prevalent in patients with moderate-severe OI. The psychosocial status of OI patients was remarkably healthy considering the severity of this disabling systemic disorder. The bodily pain complaints frequently reported in OI patients were not reflected in the orofacial area.

O17
Inflammation and increased osteoclastogenesis in osteogenesis imperfecta murine
Ivo Kalajzic, Associate Prof.
farmington, United States of America

The pathology of Osteogenesis imperfecta (OI) is mainly caused by defects in the osteoblast lineage, but there is also elevated bone resorption resulting in high bone turnover in severe forms of the disease. Consistent with this, we observed dramatically elevated serum CTX in OIM mice (>500ng/ml compared to ~20ng/ml in WT) and found splenomegaly in all ages examined (up to 20 weeks of age).

Osteoclasts originate from hematopoietic myeloid cells, however changes in hematopoiesis have not been previously documented in OI. We evaluated hematopoietic lineage distribution and osteoclast progenitor cell frequency in bone marrow, spleen and blood of OIM mice in comparison to wild-type littermates by flow cytometry.

In 7-week old male OIM animals, we identified a number of changes in hematopoietic cell frequency including expansion of the granulocyte-macrophage progenitor pool, increased myeloid lineage cells (CD11b+) in bone marrow and spleen, and reduced proportion of erythrocyte precursors (Ter119+) in the bone marrow coupled with increased frequency in the spleen. OIM spleens also showed an increased frequency of purified osteoclast progenitors (OCP, CD11bhi CD115+ Ly6Chi). This phenotype suggests chronic inflammation. Isolated osteoclast precursors from spleen and bone marrow formed osteoclasts more rapidly than WT controls.

We found that serum TNFα levels were increased in OIM, as was IL1α in OIM females. We targeted inflammation therapeutically by treating growing animals with murine TNFR2:Fc, a compound that blocks TNFα activity. Anti-TNFα treatment marginally decreased spleen mass in OIM females, but failed to reduce bone resorption as determined by serum CTX, or improve BMD or femoral bone parameters determined by μCT.

We have demonstrated that OIM mice have changes in their hematopoietic system, and form osteoclasts more rapidly even in the absence of OI osteoblast signals. OIM mice have indications of chronic inflammation but therapy targeting TNFα did not improve disease parameters.
**O18**

Collagen C-propeptide Cleavage Deficiency Increases Bone Mineralization and Alters Bone Cell Differentiation

Aileen Barnes, Biologist
Bethesda, United States of America

**Results:**
1. High Bone Mass (HBM) osteogenesis imperfecta (OI) is caused by dominant mutations in the C-propeptide cleavage site of COL1A1 or COL1A2. To elucidate the role of C-propeptide processing in bone, we generated heterozygous HBM mice with a mutated COL1A1 cleavage site to prevent cleavage by BMP1.

**Methods:**
WT and HBM bones were examined at 2-, 6- and 12-months for histology, mineralization, mechanics, and cell differentiation.

**Results:**
HBM mice are smaller than WT in weight and length. Their femoral extracts contain pC-collagen and increased monomeric COL1A1 C-propeptide, resulting in a “barbed-wire” appearance to bone collagen fibrils, thin cortices and decreased BV/TV. Collagen content is decreased in HBM femora with an increase in mature (HP) and total (HP+LP) crosslinks. HBM femora have decreased stiffness, yield and fracture load, which did not improve with age. These femora are also extremely brittle; post-yield displacement is ~15% of WT. Femoral aBMD is decreased at 2-months but is near normal at 1 year. On μCT, HBM cortical and trabecular TMD are normalized at 1 year. By qBEI, HBM cortical bone had increased CaMean, CaPeak and CaHigh at 2- and 6- and 12-months compared to WT. HBM CaPeak increased significantly between 6- to 12-months, although WT levels peaked at 6 months. Femoral Bglap transcripts are decreased, as was osteoblast collagen secretion. Osteocyte lacunar density was decreased at 2-, 6- and 12-months in HBM femora while lacunar area was increased at 2- and 6-months. HBM serum TRAP and PINP were significantly increased, consistent with increased femoral transcripts of Ctsk, Acp5 and Rankl/Opg ratio.

**Conclusion:**
Murine HBM bone mineralization is increased and keeps increasing with age, even after WT mineralization has peaked, raising concerns for long-term patient status. Alterations in multiple bone cell populations support a putative C-propeptide trimer signaling function, influencing bone matrix and mineralization.

**Objective:**
High Bone Mass (HBM) osteogenesis imperfecta (OI) is caused by dominant mutations in the C-propeptide cleavage site of COL1A1 or COL1A2. To elucidate the role of C-propeptide processing in bone, we generated heterozygous HBM mice with a mutated COL1A1 cleavage site to prevent cleavage by BMP1.

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**Conclusion:**
Murine HBM bone mineralization is increased and keeps increasing with age, even after WT mineralization has peaked, raising concerns for long-term patient status. Alterations in multiple bone cell populations support a putative C-propeptide trimer signaling function, influencing bone matrix and mineralization.

**O19**

Altered Bone Nano- and Microstructure in Osteogenesis Imperfecta caused by a C-propeptide Cleavage site Mutation

Jannie Dahl Hald, MD, PhD
Aarhus C, Denmark

**Results:**
HBM mice are smaller than WT in weight and length. Their femoral extracts contain pC-collagen and increased monomeric COL1A1 C-propeptide, resulting in a “barbed-wire” appearance to bone collagen fibrils, thin cortices and decreased BV/TV. Collagen content is decreased in HBM femora with an increase in mature (HP) and total (HP+LP) crosslinks. HBM femora have decreased stiffness, yield and fracture load, which did not improve with age. These femora are also extremely brittle; post-yield displacement is ~15% of WT. Femoral aBMD is decreased at 2-months but is near normal at 1 year. On μCT, HBM cortical and trabecular TMD are normalized at 1 year. By qBEI, HBM cortical bone had increased CaMean, CaPeak and CaHigh at 2- and 6- and 12-months compared to WT. HBM CaPeak increased significantly between 6- to 12-months, although WT levels peaked at 6 months. Femoral Bglap transcripts are decreased, as was osteoblast collagen secretion. Osteocyte lacunar density was decreased at 2-, 6- and 12-months in HBM femora while lacunar area was increased at 2- and 6-months. HBM serum TRAP and PINP were significantly increased, consistent with increased femoral transcripts of Ctsk, Acp5 and Rankl/Opg ratio.

**Conclusion:**
Murine HBM bone mineralization is increased and keeps increasing with age, even after WT mineralization has peaked, raising concerns for long-term patient status. Alterations in multiple bone cell populations support a putative C-propeptide trimer signaling function, influencing bone matrix and mineralization.

**Objective:**
High Bone Mass (HBM) osteogenesis imperfecta (OI) is caused by dominant mutations in the C-propeptide cleavage site of COL1A1 or COL1A2. To elucidate the role of C-propeptide processing in bone, we generated heterozygous HBM mice with a mutated COL1A1 cleavage site to prevent cleavage by BMP1.

**Methods:**
WT and HBM bones were examined at 2-, 6- and 12-months for histology, mineralization, mechanics, and cell differentiation.

**Results:**
HBM mice are smaller than WT in weight and length. Their femoral extracts contain pC-collagen and increased monomeric COL1A1 C-propeptide, resulting in a “barbed-wire” appearance to bone collagen fibrils, thin cortices and decreased BV/TV. Collagen content is decreased in HBM femora with an increase in mature (HP) and total (HP+LP) crosslinks. HBM femora have decreased stiffness, yield and fracture load, which did not improve with age. These femora are also extremely brittle; post-yield displacement is ~15% of WT. Femoral aBMD is decreased at 2-months but is near normal at 1 year. On μCT, HBM cortical and trabecular TMD are normalized at 1 year. By qBEI, HBM cortical bone had increased CaMean, CaPeak and CaHigh at 2- and 6- and 12-months compared to WT. HBM CaPeak increased significantly between 6- to 12-months, although WT levels peaked at 6 months. Femoral Bglap transcripts are decreased, as was osteoblast collagen secretion. Osteocyte lacunar density was decreased at 2-, 6- and 12-months in HBM femora while lacunar area was increased at 2- and 6-months. HBM serum TRAP and PINP were significantly increased, consistent with increased femoral transcripts of Ctsk, Acp5 and Rankl/Opg ratio.

**Conclusion:**
Murine HBM bone mineralization is increased and keeps increasing with age, even after WT mineralization has peaked, raising concerns for long-term patient status. Alterations in multiple bone cell populations support a putative C-propeptide trimer signaling function, influencing bone matrix and mineralization.
**Objectives**

We identified a family that clinically had mild osteogenesis imperfecta (OI), a C-propeptide cleavage site mutation in COL1A2 and high bone mineral density (BMD). We present a comprehensive investigation of the nano- and micro-structural properties of such bone to determine the extent of abnormality in this rare sub-type of OI.

**Methods**

We obtained stained, double labelled iliac crest bone biopsies from two family members. The biopsies were analyzed by histomorphometry and by advanced synchrotron radiation techniques: microtomography (µCT) (325 nm voxel size), nanotomography (50 nm voxel size) and diffraction scattering computed tomography (DSCT) (25 µm pixel size), complemented by nanoindentation and polarised light microscopy (PLM).

**Results**

Areal bone mineral densities were high in the lumbar spine and hip with mean aBMD T scores of +5.3 and +3.7, respectively. Histomorphometry showed a high BV/TV and an increased trabecular width. The bone mineral was abnormal and the apatite unit cells were larger and the crystal wider than in healthy bone. An inhomogenous organisation of collagen fibrils throughout the matrix was observed. This OI bone was highly mineralized, yet extremely porous. Distinct alternating bands of mineral density coupled with scalloped edges indicate increased bone remodelling. At the cellular level, we observed osteocyte lacunae encapsulating spherical mineralized structures.

**Conclusion/Take home message**

Our results give new insights to the bone structure and mineralization in the high BMD OI-phenotype. High resolution imaging shows severe abnormalities at all length scales with abnormal bone mineral properties and collagen organization indicating a severely impeded mineralization control. This aberrant mineralization leads to a high BMD OI-phenotype that was only detected through identification of the COL1A2 mutation. This underlines that a clinical phenotype of OI must always be confirmed by a molecular diagnosis.

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**O20**

**Murine model for type VI OI (Serpinf1-/-) reveals dynamic regulation of vascularization and mineralization in bone**

Heeseog Kang, Postdoc Fellow
Bethesda, United States of America

Heeseog Kang, Postdoc Fellow, NIH, Bethesda, United States of America; Smriti Aryal A.C., Postdoc Fellow, NIH, Bethesda, United States of America; Valentin David, Assistant Professor, Northwestern University, Chicago, United States of America; Aline Martin, Postdoc fellow, Northwestern University, Chicago, United States of America; Susan Crawford, Professor, NorthShore University, Evanston, United States of America; Joan Marini, Senior Investigator, NIH/NICHD, Bethesda, MD, United States of America

Null mutations in SERPINF1, encoding Pigment Epithelium-Derived Factor (PEDF), cause type VI osteogenesis imperfecta (OI), a progressive deforming OI with increased osteoid in vivo and delayed mineralization in vitro. Demonstration of decreased PEDF in bone with BRIL p.S40L provided evidence of a connection between types VI and V OI. PEDF was previously well-known for its potent anti-angiogenic effects. Bone vascularization is crucial for bone modeling and remodeling; endothelial cells secrete factors that affect osteoprogenitor differentiation.

We utilized RNA-seq of differentiating Serpinf1-/- calvarial osteoblasts (OB), validated by RT-qPCR, whole animal vascular perfusion and type H endothelial cells (CD31+/Endomucin+) isolated from crushed LE long bone by FACS, to explore the relationship of bone vascularization and mineralization in OI.

These studies revealed biphasic regulation of bone vascularization pathways by PEDF in osteoblasts. In PEDF-null cells, pro-angiogenic VEGF is elevated early in differentiation. However, on Day 14 of differentiation BMPER (BMP-binding endothelial regulator, which inhibits BMP-mediated VEGF transcription) is significantly increased in KO vs. WT OB, potentially compensating for VEGF elevation. In-vivo, PEDF deletion results in a significant increase in vessel density by 33% (P < 0.05) in the tibial periostium of BaSO4 perfused
KO mice. In agreement, the number of type H ECs is increased in KO mice by 18% (P < 0.05), as are type H cell VEGF and VEGFR2 transcripts, suggesting an overall pro-angiogenic effect. In contrast, decreased expression of osteoblastic markers of differentiation and mineralization Sp7, Col1a1, Ibsp, Sost and Dmp1 was observed in KO cells. Interestingly, BRIL expression is also reduced, demonstrating reciprocity of the effects of BRIL on PEDF. In line with these findings, Alizarin Red staining of KO OB yielded a delay of mineralization at Week 2 but increased mineralization at Week 4 vs. WT.

These results demonstrate complex regulation of vascularization and mineralization by SERPINF1/PEDF.

**O21**

**Zebrafish type I collagen mutants show a spectrum of skeletal phenotypes mimicking the clinical variability in OI**

Andy Willaert, PhD

Ghent, Belgium

Andy Willaert, PhD, Ghent University, Ghent, Belgium; Charlotte Gistelinck, PhD student, Ghent University, Gent, Belgium; Ronald Y Kwon, Assistant Professor, University of Washington, Seattle, United States of America; Fransiska Malfait, MD, PhD, Ghent University, Ghent, Belgium; Sofie Symoens, PhD, Ghent university, Gent, Belgium; Petra Vermassen, Technician, Ghent University, Gent, Belgium; Hanna De Saafel, Technician, Ghent University, Gent, Belgium; Shannon Fisher, Associate Professor, Boston University School of Medicine, Boston, United States of America; Katrin Henke, PhD, Harvard Medical School, Boston, United States of America; MaryAnn Weis, PhD, University of Washington, Seattle, United States of America; Anne De Paepe; Matthew P Harris, Professor, Harvard Medical School, Boston, United States of America; David R Eyre, Professor, University of Washington, Seattle; Paul Coucke

Objective: Osteogenesis imperfecta (OI) is a heritable disorder, caused by defects mainly related to type I collagen, which forms the structural scaffold of the bone extracellular matrix. Clinically, OI is characterized by a broad disease spectrum, ranging from very mild forms with minimal fractures, to severely deforming or even lethal forms. The underlying genetic basis of this variability between, but also within different types of OI, remains one of the most puzzling questions in the field. In this study we illustrate the potential of zebrafish as a tool to better understand and define genotype – phenotype correlations in OI.

Methods and Results:

We conducted a phenomics analysis of a large set of zebrafish type I collagen mutants representing different forms of OI, by mapping and quantifying numerous morphological and densitometric traits in the axial skeleton of adult zebrafish, obtained via advanced µCT-based methods. Our study revealed a remarkably high phenotypic reproducibility of the human disease features between our set of zebrafish mutants and patients with comparable genetic forms of OI. These findings, along with results from advanced computational analysis of quantitative skeletal parameters, including principal component and clustering analysis, also argued for the presence of similar genetic mechanisms, responsible for influencing the presence and penetrance of disease features, both in zebrafish models and human OI patients.

Conclusions/Take Home Message:

Recent advances in phenotypic analysis have now made it possible to perform parallel phenomic analysis of large sets of zebrafish skeletal mutants. With our study, we demonstrated that zebrafish models are able to both genocopy and phenocopy different forms of human OI, arguing for a similar genetic basis driving pathogenesis. We therefore propose zebrafish as a new tool to investigate unknown genetic modifiers and mechanism underlying the phenotypic variability in human OI.

The authors declare no commercial financial support for this work.

**O22**

**Generation of recessive osteogenesis imperfecta zebrafish models using CRISPR-Cas9 system**

Francesca Tonelli, MD

Italy

Roberta Gioia, PhD, University of Pavia, Pavia, Italy; Ilaria Ceppi, undergraduate student, University of Pavia, Pavia, Italy; Roberta Besio, PhD, University of Pavia,
OBJECTIVE
Sclerostin antibody (SclAb) is an emerging candidate to treat OI. In the Brtl/+ mouse, SclAb converts quiescent or resorbing bone surfaces to formation during growth, and can increase mineral apposition rates in aged mice. SclAb increases bone strength and stiffness, reducing susceptibility to fracture. Sequential treatment with an anti-resorptive is required to preserve bone gains, however the efficacy of SclAb, when administered concurrently with anti-resorptives, has not been shown. The purpose of this study was to identify the Brtl/+ response to SclAb when administered concurrent to bisphosphonate treatment.

METHODS
21-day male Brtl/+ and WT mice received a single dose of pamidronate (PAM, 0.3, 0.625 mg/kg) followed three days later by two weeks of SclAb (25 mg/kg, 2x/wk). This cycle was repeated, and 8-wk combined treatment animals were compared to controls treated with saline, PAM, or SclAb alone.
RESULTS
PAM alone dose-dependently increased trabecular number in the distal femur (+29-45%) and lumbar vertebrae (+8-14%), with no effect on trabecular thickness. Conversely, SclAb led to trabecular thickening (+33%), and a retention of trabecular number alone (+39% femur, +15% vertebra), or when combined with PAM. PAM did not interfere with SclAb-induced trabecular or cortical thickening. Mid-diaphyseal gains in stiffness and ultimate load were attained by SclAb. Vertebral ultimate load was improved by SclAb, without further gains when combined with PAM. However, vertebral stiffness showed synergistic gains with both treatments together.

CONCLUSION
SclAb induced cortical and trabecular thickening, while PAM acted to increase trabecular number. Combined therapy induced synergistic gains in trabecular mass and vertebral stiffness, suggesting a distinct advantage of both therapies combined.

TAKE HOME MESSAGE
Combining traditional anti-resorptive therapy with SclAb may have long-term benefits for decreasing bone fragility at trabecular sites in OI patients.

DISCLOSURES
Funding: NIH AR062522. SclAb: Amgen Inc (Thousand Oaks, CA, USA) and UCB (Brussels, Belgium).

O24
Cathepsin K knockout reduces fracture incidence and improves trabecular bone mass and microarchitecture in the axial skeleton of oim/oim mice

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Belgium

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Objective
The oim/oim mouse is a well-accepted model of human type III OI, the most serious form compatible with postnatal survival. As Cathepsin K (CatK) deletion and inhibition enhance bone mass and strength, we bred CatK KO mice (CatK-/-) with oim/oim mice to assess the effect of CatK loss on the bone mass and strength of resulting OI mice.

Experimental approach:
We selected wild-type control mice (Wt/Wt), CatK -/- mice, oim/oim mice (oim -/-), and oim/oim mice KO for CatK (oim/oim CatK-/-). After sacrifice at 13 weeks of age, the axial skeleton radiographed with soft X-rays and scanned with a Stratec XCT Research SA+ pQCT. Quantitative micro-computed tomography (µCT) measured cancellous bone of the fifth lumbar vertebra (L5).

Results
Pelvic fractures were solely present in oim/oim mice. Wt/Wt and CatK -/- mice were free of tail fractures while oim/oim CatK-/- mice had a 67% reduction in tail fractures compared to oim/oim mice. With pQCT, oim/oim CatK-/- mice increased their BMD in the cervical spine (+13%), thoracic spine (+16%) and lumbar spine (+23%) as compared to oim/oim mice. Further comparison between the two types of oim/oim mice by using µCT of L5 showed that oim/oim CatK-/- mice had 38% decrease in the space between trabeculae and an increase in bone volume density (+90%), trabecular number (+95%) and connectivity density (+135%).

Conclusion
CatK KO markedly reduces the pelvic and tail fracture rates in oim/oim mice without affecting their abnormal type I collagen molecules. The improvement in bone mass and microarchitecture likely contributes to the positive impact on bone strength. Accordingly, CatK inhibition is a promising therapy for human type III OI.

O25
Screening for osteogenic compounds using the zebrafish as a model

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Objectives
The pharmacological therapy of choice in fragile bone disorders is based on bisphosphonates, which inhibit osteoclast-mediated bone resorption. However, this only prevents deterioration of existing bone. Therefore drugs are required that combine anti-resorptive and anabolic action, thus improving bone quality. Although some compounds have already shown promising effects in mouse models, these results are highly variable due to the limited number of animals that can effectively be screened in these models. Therefore, there is a need to assess the effect of promising new osteogenic drugs in larger sets of animal models for fragile bone disorders, using a standardized higher throughput workflow.

Methods
In this work we assessed the feasibility of different readouts for mineralization and bone formation in zebrafish larvae, combined with administration of osteogenic compounds. The zebrafish is considered as an excellent tool for high-throughput compound screening because of the low cost, external fertilization and the generation of large numbers of rapidly developing transparent embryos that can be treated with compounds via the water.

Results & Conclusion
Two drugs that were previously shown to increase bone formation in zebrafish larvae, 1α,25-dihydroxyvitaminD3 and teriparatide, were used as positive controls in the development of a phenotypic readout. These readouts include in vivo monitoring of larval mineralized structures through alizarin red staining in combination with transgenic reporter lines for osteoblasts and osteoclasts. This analysis is supplemented with measurements of alizarin red fluorescence through spectrophotometry and mRNA expression analysis of different markers for mineralization and bone formation. These methods will enable future screens of promising osteogenic compounds in zebrafish models for fragile bone disorders.

Take home message
The zebrafish is a platform that allows for quick screening for osteogenic compounds.

O26
Characterization of Chihuahua as a dominant osteogenesis imperfecta zebrafish model and its use in new pharmacological approaches.
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Pavia, Italy

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Objectives.
Dominant forms of Osteogenesis imperfecta (OI) are mainly caused by collagen type I mutations and characterized by bone fragility and growth delay. Nowadays no definitive cure is available for OI. A zebrafish OI model (Chihuahua) carrying a heterozygous G574D substitution in the α1 chain of collagen type I has been used to perform pharmacological screening. Since mutant collagen is intracellularly accumulated in OI, chemical chaperones were tested.

Methods.
The morphology of zebrafish Chihuahua (chi+/+) before and after treatments was analyzed by histological staining, x-ray analysis and μCT. Mutant collagen type I was characterized by SDS-PAGE and DSC. ER stress was evaluated by transmission electron microscopy, confocal microscopy and immunohistochemistry. qPCR, Western Blot and Picro Sirius Red staining were used to uncover the drug mechanism of action. Results. X-ray, μCT, alcian blue / alizarin red and calcein staining revealed severe skeletal deformity, fractures and delayed mineralization in
mutant fish. Collagen I from different tissues showed abnormal electrophoretic migration and low melting temperature. The presence of ER enlargement due to mutant collagen retention was demonstrated in mutant osteoblasts and fibroblasts. Two chemical chaperones 4PBA and TUDCA were used to ameliorate the cellular stress using a short-term treatment for larvae and a long-term treatment for adult fish. 4PBA ameliorated bone mineralization in larvae and skeletal deformities in adult mainly acting on reducing ER cisternae size and favoring collagen secretion.

Conclusions.
Our data validated chi/+ as a model for classical OI and we demonstrated that cellular stress is a novel target to ameliorate OI phenotype. Chemical chaperones such as 4PBA may be, alone or in combination, a new class of compounds to be further investigated for OI therapy.

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O27
Use of induced pluripotent stem cells and CRISPR/Cas9 in Osteogenesis Imperfecta: first results
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Rationale and objective:
In approximately 90% of patients with osteogenesis imperfecta (OI) the genetic defect concerns dominant pathogenic variants in the COL1A1/2 genes encoding collagen type I (COL1). Pathogenic variants lead to a 50% decrease of normal COL1 production or production of abnormal COL1. Current therapy mainly consists of conservative management and/or bisphosphonate therapy, which inhibits osteoclast activity and is as such not aimed at the primary defect in OI. The main objective is to conduct preclinical studies that eventually result in functional improvement of bone in OI patients.

Methods:
Skin biopsies and urine samples from 6 adult patients with a clinical diagnosis of OI type 1, 3 or 4 and an identified pathogenic COL1A1 or COL1A2 variant were collected in the expert center for adults with OI in Isala, Zwolle, the Netherlands.

Results:
Patient urine-derived epithelial cells were isolated and successfully reprogrammed to generate induced pluripotent stem cells (iPSC). A CRISPR/Cas9-based strategy has been developed to repair the c.1588G>A OI causing-mutation in patient-specific iPSC, work performed at the iPSC-CRISPR Facility, Groningen, the Netherlands.

Conclusion:
We report the first results of our research strategy combining patient-specific iPSC and gene-correction through CRISPR/Cas9, with the aim to improve bone functionality in OI patients.

Take home message:
Patient-derived stem cells in combination with genome editing may potentially advance the treatment of OI patients in the future.

O28
Physical activity levels and perceived barriers to participation of children with Osteogenesis Imperfecta.
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Physiotherapist, Macquarie University, Macquarie University; Annabel Price, Physiotherapist, Macquarie University, Macquarie University, Australia; Anna Chmielewski, Physiotherapist, Macquarie University, Macquarie University; Max Lozano, Physiotherapist, Macquarie University, Macquarie University, Australia; Craig Munns, Associate Professor, The Children’s Hospital at Westmead, Westmead, Australia; Verity Pacey, Senior Lecturer & Senior Physiotherapist, Macquarie University & The Children’s Hospital at Westmead, Macquarie University, Australia

Objectives:
To quantify the level of physical activity performed by children with Osteogenesis Imperfecta and identify barriers to physical activity as perceived by children and their parents.

Methods:
Fifty-four children aged 7-17 years, with a confirmed diagnosis of mild, moderate or severe Osteogenesis Imperfecta were recruited for this study. The Actigraph GT3XE was used to record average daily moderate-vigorous physical activity, and the ActivPAL3 was used to record average daily time spent sitting, standing, stepping and average daily step count. Child and parent specific questionnaires examined barriers to physical activity.

Results:
Wear time eligibility for the Actigraph GT3XE and ActivPAL3 was achieved in 28 and 32 children respectively. Forty-six percent of participants met the current guidelines of 60 minutes/day of moderate-vigorous physical activity, and 25% of participants achieved the recommended step count for children of a minimum of 12,000 steps/day. Health professional recommendations to restrict physical activity was the most frequently child-reported barrier (73%), and the second most frequently parent-reported barrier (70%). The most frequently parent-reported barrier was that physical activity will cause their child pain (76%). There was no association between overall number of barriers reported and physical activity ($r = -0.001, p = 0.99$).

Conclusions:
This is the largest study examining physical activity in children with Osteogenesis Imperfecta, with most children not reaching national physical activity recommendations. Health professional recommendations to restrict physical activity are perceived as a significant barrier to physical activity participation.

Take-home messages: Further facilitation of safe physical activity for children with Osteogenesis Imperfecta, while continuing to minimise fracture risk, warrants further consideration.

O30
Osteogenesis Imperfecta Foundation: New Strategies in Advancing Education of Individuals, Families and Healthcare Providers
Tracy Hart, CEO
Gaithersburg, United States of America

The Osteogenesis Imperfecta Foundation (OIF) is committed to improving the quality of life for individuals affected by OI through research, education, awareness and mutual support. As a partner of the Brittle Bone Disorders Consortium (BBDC), the OIF concentrates on three strategies to fulfill the consortium’s education and training components: (1) developing new informational materials for medical professionals and constituents, (2) facilitating training opportunities at professional society meetings, and (3) expanding the OIF regional conference program to align with BBDC research sites.

The OIF has developed informational materials for medical professionals including fact sheets, newsletters, and podcasts that discuss OI types, diagnosis, newborn care, multidisciplinary treatment, pregnancy, pulmonary issues, orthopedic care and the latest research updates. These resources have been accessed 23,000 times by individuals from 45 countries across the world. A new Take Charge of Your Health Toolkit for adults was also developed and has been distributed to over 2,000 community members in print and online. These tools together are complementary, aiming to help individuals living with OI partner with their doctors to be informed, proactive healthcare consumers.

The OIF engages with other advocacy groups and professional societies to distribute these new resources and also coordinates training.
workshops. Within the past year, the OIF has engaged over 4,000 physicians and researchers at the American Society for Bone and Mineral Research, American Society for Anesthesiologists, Endocrine Society, American College of Emergency Physicians, National Osteoporosis Foundation, and the International Meeting on OI.

Additionally the OIF expanded the one-day regional conference program to bring updated medical information and resources to people near their homes. Since 2015, the OIF regional conference program has reached 703 individuals and received positive feedback from 99% of respondents. Over 50% of participants attended an OIF event for their first time, demonstrating the need and demand for more community outreach.

O31
Preventative Care and Treatment in Osteogenesis Imperfecta: What role for Clinical Psychology?
Megan Riddington, Dr
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Objectives
To demonstrate Clinical Psychology’s contribution to meeting the holistic needs of children/families overseen by the National, Highly Specialised, Childhood Osteogenesis Imperfecta (OI) Service in England.

Methods
1. Development of Services - Positioning Clinical Psychology within existing service structures across the four Highly Specialised OI Regional Centres and identifying core roles/responsibilities.
2. Contribution of psychological assessment/intervention to the care and treatment of children/families, demonstrated with worked case examples.


Results
1. The service structure, roles and activities of clinical psychology across the Highly Specialised OI Regional Centres in England remains idiosyncratic. The core principle of preventative care, grounded within a collaborative, multidisciplinary approach however guides psychology delivery across all Centres. Psychologist work directly and indirectly, within both inpatient and outpatient settings, integrated within the MDT, and in partnership with the child/family and local network. Interventions are delivered with individuals, families and groups.

2. Irrespective of OI severity, psychology assessment/intervention contributes across multiple areas of clinical need, including: Trauma & Recovery, Adjustment & Attunement, Mental Health Difficulties, Developmental Difficulties, Identity Development and Difference, Fatigue/Pain, Adherence and Procedural Anxieties. Reduced distress, increased coping and resilience, and improved participation and functioning represent positive outcomes, in line with agreed goals of the child/family. Shared formulations with the child/family, MDT and local network, enable a whole team approach to holistic care, taking into account psychological difficulties that can be a barrier to effective medical treatments.

3. New screening protocols employing both quantitative and qualitative measures help identification of in-need families, and prioritising of limited psychological resource.

Conclusion
The provision of clinical psychology is valuable in meeting the holistic needs of the OI paediatric population and supporting the medical team in provision of care.

Take Home Message
Clinical psychology supports holistic care in OI.
O32
Insights into bone phenotype and collagen biochemistry of TMEM38B null mutations causing Type XIV OI
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Objectives:
Recessive osteogenesis imperfecta (OI) type XIV is caused by null mutations in TMEM38B, encoding TRimeric Intracellular Cation channel type B (TRIC-B), which is involved in calcium release from the ER. The pathophysiological mechanisms of Type XIV OI remain poorly understood. We report on clinical phenotype and cellular defects in eight individuals from five unrelated families.

Methods:
Bone phenotype was characterized in three transiliac biopsy samples. Intracellular calcium dynamics, collagen biochemistry and gene expression were studied in proband and control fibroblasts and osteoblasts and murine osteoclasts.

Results:
Clinical phenotype was highly variable even among siblings, ranging from asymptomatic to severe OI with multiple vertebral and/or non-vertebral fractures; all patients were osteopenic. Median lumbar spine BMD was -3.3 [range -4.77 to +0.1]. Muscle hypotonia and cardiac abnormalities were also found.

All TMEM38B mutations resulted in undetectable TRIC-B protein in osteoblasts and fibroblasts. TRIC-B deficient cells showed low total calcium, but normal ER steady-state calcium, reflecting decreased flux from ER to cytoplasm. Low calcium flux activated PERK-mediated ER stress response. Biopsy samples revealed decreased trabecular volume and osteoclast number, low-normal osteoblasts and bone matrix mineralization within normal range. Osteoblast differentiation in vitro showed reduced expression of early markers, but increased expression of late markers, including those related to mineralization. High TRIC-B expression in murine osteoclasts suggests TRIC-B mutations may affect osteoclasts directly. The altered calcium status also affects multiple
enzymes involved in collagen interactions and modifications, leading to significant underhydroxylation of lysine, retention of collagen intracellularly and collagen insufficiency in matrix. Conclusion and take home message: The disrupted calcium flux from the ER in type XIV OI alters bone cellular parameters, osteoblast differentiation and collagen synthesis, modification and secretion. The paucity of osteoblasts and osteoclasts, along with normally mineralized bone matrix, suggest a unique OI phenotype, possibly including an intrinsic osteoclast defect.

**O33**

Severe Osteogenesis Imperfecta presentation in a family with a novel CREB3L1 mutation

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Objectives
The identification of new genetic variants for Osteogenesis Imperfecta (OI) is necessary in order to improve patient diagnosis as well as to understand the basis of disease pathology. We report a nonconsanguineous family in Indonesia of Balinese descent with severe OI. Three of the six siblings presented OI manifestations such as short stature, scoliosis of vertebrae thoracals, joint contractures and frequent fractures since childhood. In addition they showed very severe tibia bending resulting in bone protrusion. Physical examination revealed the unilateral absence of the humerus in two of the three brothers. Both parents and the rest of the siblings showed no symptoms. Our objective was to identify the causative OI mutation in this family.

Methods
Saliva was obtained from three affected and one unaffected sibling of the family which was used to isolate gDNA. Genetic testing was performed by targeted next generation sequencing in the VU medical centre for the available panel of known OI genes.

Results
We identified the homozygous mutation c.1365del p.(Pro458Argfs*25) in the three affected brothers which was absent from the healthy brother. This gene encodes the ER-stress transducer OASIS. The mutation is predicted to lead to a null allele due to nonsense mediated decay.

Conclusion
This is the second report of a causative recessive OI mutation in CREB3L1. Consistent with the first report, which identified a genomic CREB3L1 deletion, the affected members of our family also presented very severe bone deformities. However, in contrast to the first report in which patients did not reach adulthood, the patients of this family survive until now despite severe physical disability.

«Take home message»
We identified the novel c.1365del p.(Pro458Argfs*25) mutation in CREB3L1 causing severe recessive OI in a family with adult survivors. This confirms CREB3L1 as a causative gene in severe OI.

**O34**

Defective Regulated Intramembrane Proteolysis (RIP) due to mutations in MBTPS2 underlies X-linked Osteogenesis Imperfecta (OI)

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Objective:
In two pedigrees with apparent X-linked inheritance of OI, affected males have a moderate/severe phenotype with pre- and postnatal fractures of long bones and ribs, dysplastic bone with crumpling and bowing, pectal deformities, scoliosis, short stature, and reduced bone density. Our goal was to elucidate the causative gene, its mechanism and relationship to collagen.

Methods:
We utilized linkage and next generation sequencing, RT-PCR, western blots, collagen metabolism studies in cells, urinary biomarkers and mass spectrometry of bone extracts

Results:
We identified unique missense mutations (p.N459S or p.L505F) in the X-linked gene MBTPS2 in each OI pedigree (X-OI). X-OI males do not have symptoms of IFAP, a condition previously identified in MBTPS2. MBTPS2 encodes site-2 protease (S2P), localized in the Golgi membrane and coordinating the sequential cleavage of regulatory proteins during cell stress with S1P. Residues N459 and L505 are located in or near the S2P metal ion coordination motif, affecting regulated intramembrane proteolysis (RIP) activity but not MBTPS2 expression or S2P stability. Cleavage of RIP substrates, OASIS, ATF6 and SREBP, were markedly impaired in X-OI fibroblasts (FB) and osteoblasts (OB), as in IFAP FB. Despite impaired OASIS cleavage, collagen expression was normal in L505F OB. Both X-OI and IFAP mutations reduced collagen secretion. Collagen from X-OI bone tissue had reduced K87 hydroxylation, critical for collagen crosslinking in matrix. The reduced hydroxylation corroborated the elevated urinary LP/HP crosslink ratio in affected males, but not X-OI carrier females or IFAP patients. OB from X-OI also had defective differentiation in vitro, with reduced transcripts of ALPL, CREB3L1/OASIS, SMAD4 and MATN1.

Conclusions:
Type XVIII OI, caused by defects in MBTPS2, is the first X-linked OI type. X-OI is collagen-related because collagen modification and cross-links are abnormal. These data, plus prior work on S1P and OASIS, establish a role for RIP in skeletal formation.

O35
FAM46A mutations are responsible for autosomal recessive form of Osteogenesis Imperfecta
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Stuve-Wiedemann syndrome (SWS) is characterized by bowing of the lower limbs, respiratory distress and hyperthermia often responsible for early death. Survivors develop progressive scoliosis and spontaneous fractures. We previously identified LIFR mutations in most SWS cases but absence of LIFR mutations in five patients led us to perform exome sequencing and to identify homozygosity for FAM46A mutation in one case [p.Ser205Tyrfs*13]. The overlap between SWS and Osteogenesis imperfecta (OI) prompted
us to screen the FAM46A gene in 25 OI patients with no known mutations. We identified a homozygous variant in FAM46A in two affected sibs with typical OI [p.His127Arg]. FAM46A is a member of the superfamily of nucleotidyl transferase fold proteins but its exact function is presently unknown. RT-PCR analysis detected a specific expression in human osteoblasts. Interestingly, a non-sense mutation in Fam46a has been recently identified in an ENU-derived mouse model characterized by short stature, skull deformities and reduced cortical thickness in long bones. We conclude that FAM46A mutations are responsible for a form of osteogenesis imperfecta with bowing of the lower limbs and we suggest screening this gene in unexplained OI forms.
Abstracts - Posters

P2
Bone histological features in X-linked osteoporosis patients with loss of function PLS3 mutations
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Objectives
We discovered loss of function mutations in PLS3 to cause X-linked osteoporosis and fractures adding one more candidate to the gene repertoire of Osteogenesis Imperfecta (OI). However, the underlying mechanism leading to disease development remains unknown. PLS3 encodes T-plastin, an actin bundling protein highly abundant in osteocyte processes, which are important for mechanosensing. We hypothesize that the pathological bone phenotype is caused by the PLS3 mutations by affecting the function of osteocytes in sensing mechanical loading and subsequently controlling bone remodeling and deposition of collagen by osteoblasts. Our objective was to investigate histomorphometric parameters of bone turnover and mineralization in two patients with loss of function PLS3 mutations.

Methods
Transiliac bone biopsies were obtained from two male patients with hemizygous PLS3 mutations. These mutations (c.1050_1053del and c.235delT) are shown to lead to nonsense mediated decay and no protein expression. Five micrometer thick sections from undecalcified bone samples were stained for Goldner’s Trichrome and TRAcP according to standardized methods for analysis of bone structure and bone turnover. The results were compared to bone tissue from Crohn’s disease patients.

Results
Qualitative analysis of the two patients revealed relatively normal cortical thickness with high porosity. Trabecular structure was hardly present, but showed numerous osteoid seams and large multinucleated TRAcP positive cells. Osteocyte density was high with relatively large osteocyte lacunae. Bone matrix was lamellar with thin lamellae.

Conclusion
Histomorphometric examination of patients with loss of function PLS3 mutations revealed impaired trabecular bone structure and high bone turnover. High osteocyte density may indicate impaired osteocyte morphology. Shorter dendritic processes might cause the osteocytes to stay in close proximity to each other to maintain their communication network. Thin lamellae indicate impaired matrix, likely owing to dysregulated collagen production by osteoblasts.

«Take home message»
PLS3 mutations affect mechanosensing and osteoblast collagen production/deposition.

P3
Delineation of the mechanism mediating Osteogenesis Imperfecta presentation in IFITM5 mutations
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Objectives
IFITM5 (interferon-induced transmembrane protein 5) regulates mineralization; mutations cause autosomal dominant Osteogenesis Imperfecta (OI) with variable clinical presentation. Interestingly, two reported IFITM5 point mutations present different clinical manifestations indicating a
different pathological mechanism. The c.-14C>T mutation results in the addition of 5 amino acids at the N-terminus of IFITM5; this mutation leads to OI type V with hyperostosis. The c.119C>T mutation in the coding region causes a serine to leucine substitution (p.S40L) and promotes a more severe OI type III resembling phenotype. The objective was to address phenotypic differences in bone by investigating the efficiency of osteoblastic differentiation in patients with the c.119C>T mutation.

Methods
Fibroblasts from two OI patients with the c.119C>T mutation and from three age-matched healthy controls were subjected to osteogenic transdifferentiation for 21 days using a growth factor-based protocol. The efficiency of osteoblastic differentiation was evaluated based on the expression of osteogenic markers RUNX2, ALP and COL1A1. In vitro mineralisation was assessed both with alizarin red and von Kossa staining. The expression of P3H1, CRTAP and PPIB was also quantified at the mRNA and protein level.

Results
Cells from patients with the c.119C>T mutation showed higher potential for osteogenic differentiation compared to the healthy controls based on the higher expression of RUNX2 on day 10 and 21 and of ALP on day 10 which correlated with increased CRTAP expression. No differences were found in COL1A1, P3H1, PPIB and CRTAP expression at the mRNA level. The mineralization pattern varied between patients.

Conclusion
We have shown that the c.119C>T mutation increases the capacity of OI fibroblasts for osteogenic transdifferentiation. In the same experimental setting, we are currently investigating the effect of the c.-14C>T mutation on osteogenesis.

«Take home message»
The role of IFITM5 in OI extends beyond mineralization to osteoblast differentiation regulation.

P4
Bone Robusticity in Osteogenesis Imperfecta Diverses from Established Patterns
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PURPOSE:
Osteogenesis Imperfecta (OI) occurs in 1/10,000 live births with severity ranging from perinatally lethal to mild forms with minimal fractures. To investigate bone morphology, we calculated robustness (Tt.Ar/Le) and relative cortical area (RCA = Ct.Ar/Tt.Ar) from measurements of the second metacarpal and compared these measurements to age-matched controls. We hypothesize that OI patients will have reduced robustness (i.e. slenderness) compared to controls and that bisphosphonate treatment will not impact bone robusticity.

METHODS:
A retrospective review of 83 de-identified bone age films identified 58 OI patients (1 year 9 mos.- 67 yrs.) and 37 controls (4 year 6 mos.-21 yrs.). Non-parametric Kruskal-Wallis tests were used to compare differences between groups with statistical significance at p≤0.05.

RESULTS:
OI patients had RCA values above and robustness values below that of the control population (p<0.001, table 1), independent of treatment. Bisphosphonate treatment did not change morphologic parameters in OI patients. In contrast to that reported in the unaffected population, sexual dimorphism was not significant in the OI patients for either robustness or RCA.
CONCLUSION:
Given the mechanistic link between type I collagen and bone strength, we suggest that the underlying collagen abnormalities in OI override sex-specific effects on bone development. The reduced bone mass of OI seems to come from suppressed periosteal expansion (lower Tt.Ar, table 1) and not failure to accumulate bone mass (RCA was appropriate for the slender phenotype). Because slender bones are structurally weaker than more robust bones, OI patients have both a material and a structural problem contributing to their overall strength deficit. Understanding these patterns of bone morphology is important in predicting how patients will respond to treatment and to optimize the treatment effect.

SIGNIFICANCE:
Treatment for OI patients should focus on periosteal expansion (not suppressing resorption) to strengthen long bones.

P5
Bone Characteristics of Otic Capsule in oim/oim Mouse Model
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Purpose:
Osteogenesis Imperfecta (OI) is a group of heritable disorders characterized by increased bone fragility. Clinical features may include fractures, blue sclera, cardiopulmonary abnormalities, and hearing loss. Treatment with bisphosphonates in non-OI patients has shown to decrease hearing loss. This study was conducted to determine whether various treatments influence the bone quality and characteristics of otic capsule in OI Type III-equivalent mouse strain.

Methods:
Homozygous (oim/oim) and WT mice were treated with saline, RANK-Fc, or alendronate, starting at 2 weeks. After 12 weeks, half of the mice receiving saline and half of the mice receiving ALN began treatment with RANK-Fc. Treatment ended at 24 weeks. Femur and cochlea were scanned using Scanco-35 microCT. T-test was used for means comparisons.

Results:
There were significant baseline differences in BV/TV and Bone Th. Treatment with ALN+RANK of male oim/oim mice increased BV/TV, Bone Th., and apparent density. Females had lower BV/TV, Bone Th., TMD, and apparent density than males for various treatment modalities. Femoral cortical bone parameters did not mirror otic capsule.

Conclusions:
Ear bones and femur cortical bone are significantly different in bony characteristics and composition. Sexual dimorphism may be present in bone characteristics of otic capsule in oim/oim mice. Whereas femurs in the oim/oim saline-treated mice display characteristics of osteoporosis and osteopenia as compared to WT mice, the ear does not display these characteristics. Thus, there seems to be no obvious ear phenotype in oim/oim mice.

Significance:
Bone of the otic capsule is unlike the cortical bone of the femur. Bisphosphonate treatment may improve hearing loss. Treatment options for and data regarding natural history of hearing loss are scarce. That the bones in the ear may differ from cortical bone in oim mice is significant.

P7
Dentinal collagen mutations in children with Osteogenesis Imperfecta
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Purpose:
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Conclusions:
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Significance:
Bone of the otic capsule is unlike the cortical bone of the femur. Bisphosphonate treatment may improve hearing loss. Treatment options for and data regarding natural history of hearing loss are scarce. That the bones in the ear may differ from cortical bone in oim mice is significant.
Introduction:
Osteogenesis Imperfecta associated with Dentinogenesis Imperfecta (DI type I) and Dentinogenesis Imperfecta in teeth alone (DI type II) are genetic disorders that affect the ultrastructure of collagen fibrils present in dentine. The OI clinic at Great Ormond Street Hospital has long established links with the Eastman Dental Hospital for dental screening, and has audited this service since September 2011. The nanostructure of dentin in OI and DI has been a strong focus of the anomalies research team.

Aim:
To investigate changes in collagen ultrastructure and assess the possible impact in the overall physical properties of dentine in primary teeth.

Methods:
A demineralisation protocol was established and verified using FTIR, to monitor the ratio of Amide I/II (collagen) bands with the Phosphate band (Hydroxyapatite HA). SEM and AFM were using to assess collagen fibrils and measure d-band periodicity. Hardness was calculated using a Wallace indenter.

Results:
Nine primary teeth were analysed (3 Control, 3 DI I & 3 DI II). SEM images compared the control samples before and after demineralisation protocol - images showed smooth debris free surfaces with unclogged, well-formed dentinal tubules and collagen fibrils with no sign of acid-damage. D-banding was clearly observed and homogenous using AFM (~71.4nm). Collagen fibril networks in DI Type I samples were identified but D-banding periodicity was not measureable. In DI type II, collagen fibrils were difficult to identify with spherical mineralized structures noted. The value of dentine hardness significantly decreased in DI Type I and II when compared to the control group.

Conclusion: The dentine hardness in DI Types I & II is reduced when compared to normal primary teeth. There is a correlation between the hardness of dentine and the mineral content of its structure. On a microscopic level there were evident differences in collagen structure between the three groups.

Objectives
This study is focused on the molecular genetic analysis of selected coding sequences of COL1A1 gene in three unrelated patients (two men and one woman) affected by osteogenesis imperfecta (OI) type III, the most severe nonlethal form of OI. Clinical features observed in described patients include short stature, severe bone deformities, low bone density, “popcorn-like” calcification of epiphyses, barrel chest and dentinogenesis imperfecta.

Methods
DNA samples were extracted from the leucocytes of peripheral blood and analysed using polymerase chain reaction and Sanger sequencing methods. Obtained data were compared to the wild-type sequence as submitted to Ensembl accession no. ENST00000225964. Identified DNA changes were compared with the Osteogenesis Imperfecta Variant Database, collagen type I, alpha I (COL1A1), the Ensemble database and the Human Genome Mutation Database.

Results
Previous analyses were focused on COL1A1 exons selected using high resolution method (HRM). These analyses identified one mutation, p.Cys61Phe (Hruskova et al. 2016). We are currently analysing remaining COL1A1 exons to identify possible disease causing DNA changes of described individuals.
Conclusion
Patients with unaffected alpha1(I) chain synthesis will be included in a subsequent study focused on COL1A2 (collagen type I, alpha 2 chain) coding sequences analysis or on other genes (IFITM5, SERPINF1, CRTAP, P3H1, PPIB and other) involved in genetic origin of another autosomal dominant or recessive OI forms.

The clinical and genetic heterogeneity of OI manifests not only within one OI type but also between individual forms. For that reason, genotype-phenotype correlation is crucial for understanding the possible impact of concrete DNA changes on the clinical outcome of individual patients.

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P9
The COL1A1/2 mutational spectrum in Estonian, Ukrainian and Vietnamese Osteogenesis Imperfecta patients.
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Osteogenesis Imperfecta (OI) is caused by collagen I quality or quantity defects. Amount of collagen I mutations was 50-90% in different studies.

The main aim of the current study was to investigate mutational spectrum of collagen I mutations in OI patients from Osteogenesis Imperfecta database of Tartu University Department of Traumatology and Orthopaedics and compare data in different populations.

We have performed Sanger sequencing of the COL1A1 and COL1A2 genes from the whole blood gDNA of 196 unrelated OI patients of Vietnamese (91 patients), Ukrainian (76) and Estonian (29) origin. Primers were design to capture all exons, splice sites and 5'UTR, 3'UTR regions. Sequence reads were analyzed and their pathogenicity was predicted in silico. Mutations were checked towards normal databases. Novelty of mutations was controlled in OI mutation database. Percentage differences were calculated to compare OI populations.

Total percentage of COL1A1/2 mutations in all investigated patients was 65.3% (128/196). Detailed analysis of OI population discovered COL1A1/2 mutations in 59.4% (54/91) of Vietnamese, 64.5% (49/76) of Ukrainian and 86.2% (25/29) of Estonian OI patients. Number of COL1A1 mutations was bigger in all three OI populations, as expected. Estonian OI patients harbored mostly nonsense and splice site mutations, making quantity collagen defect to be the cause of OI in 72% of Estonian patients. In Ukrainian OI, population number of quality and quantity was almost equal (49.0% and 51.0%). Interestingly, all mutations of Ukrainian OI patients were in heterozygous state. Vietnamese OI patients had the highest number of quality mutations, 81.5%. Percentage of novel mutations was 48.0% in Estonian, 34.7% in Ukrainian and in 50.0% in Vietnamese OI patients.

In conclusion, percentage of COL1A1/2 mutations varied between Vietnamese, Ukrainian and Estonian OI patients from 59.4% to 64.5 and 86.2%, respectively. Moreover, we highlighted differences in spectrum of COL1A1/2 mutations among studied populations.

P11
Study of pulmonary function in Osteogenesis Imperfecta
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Objective:
To describe the respiratory pattern of patients with Osteogenesis Imperfecta.
Methods:
Transversal study was conducted and inclusion criteria were diagnosis of OI and age 5 years old or older. Clinical characteristics and pulmonary function as forced vital capacity (FVC), forced expiratory volume in one second (FEV1), maximum midexpiratory flow (MMEF) were measured by spirometry. Respiratory muscle strength (maximal inspiratory pressure [MIP] and maximal expiratory pressure [MEP]) were also evaluated by manovacuometry.

Results:
We evaluated 41 patients (62.5% female), median age 13.7 years (25-75 percentiles 9.8-22.9 years). Most cases presented OI type I (50%), followed by type IV (35.0%) and type III (15.0%). 65.0% patients were able to walk independently, 25.0 % were restricted to wheelchair, 5.0% were able to walk short distances with or without assistance and 5.0% were able to walk at home with or without assistance. Of the 41 patients evaluated, 33 performed spirometry. FVC: 2.22 ± 0.98L (0.70 – 4.19); FEV1: 1.99 ± 0.93L (0.0 – 3.71) and MMEF: 2.69 ± 1.3 (0.66 – 5.37). There was significant difference between mild versus moderate/severe OI type for MMEF (p=0.042) however, FVC and FEV1 there was no significant association (p=0.087).

Conclusions:
This study showed that moderate/severe forms of OI have low MMEF. We reinforce the importance of respiratory evaluation in OI patients to trace strategies that help their management throughout life.

Take home message:
Pulmonary evaluation is important in OI, especially in moderate/severe forms.

Financial suppor: FIPE/HCPA and CNPq

P12
Cardiovascular involvement in Children and Adults with Osteogenesis Imperfecta
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Objective:
Our purpose was to investigate cardiovascular characteristics in Osteogenesis Imperfecta (OI).

Methods:
Transversal study was conducted, and inclusion criteria were diagnosis of OI and age 5 years old or older. M. mode color Doppler and pulsed Doppler echocardiography was done by a cardiologist.

Results:
We evaluated 71 patients, 43 children/adolescents from 5-18 years old with median age of 13.0 (25-75 percentiles 8-14.4) and 28 adults with median age of 28.55 (25-75 percentiles 21.6-52). Female corresponded to 48.2% children/ adolescents and 67.9% adults. In the children/adolescents group most cases presented OI type I (69.8%) followed by type IV (20.9%), type III (7.0%) and type V (2.3%). In adults group most cases presented OI type I (64.3%), followed by type III (14.3%), type IV (10.7) and type V (10.7%). In the children/adolescents group mean EF was 69.9 ± 5.66% and SF was 38.69 ± 6.77%. One patient (2.3%) had mild mitral regurgitation and one patient (2.3%) mild tricuspid regurgitation. In adults, mean EF was 67.3 ± 4.2% and SF was 37.2 ± 3.1%. One patient (3.6%) was diagnosed with patent foramen ovale (PFO), two (7.1%) patients had mild aortic valve insufficiency and one (3.6%) adult had mitral and aortic insufficiency and undergone mitral valve repair and aortic valve replacement at age 47. Moreover, 5 (17.9%) patients suffered from mild tricuspid regurgitation with gradients of 18 – 35 mmHg.
Conclusion:
Extra bone involvement has been recognized as clinical finding in OI. Cardiovascular is one of the manifestations of the disease and can occur even without the presence of clinical symptoms. Cardiac valve involvement is common especially in adults and all patients with OI should have a routine cardiovascular system evaluation.

Take home message:
Cardiovascular is an extra bone manifestation especially in adults with OI and should be evaluated.

Financial supported: FIPE/HCPA and CNPq.

P13
ECOCARDIOGRAPHY STUDY IN CHILDREN WITH OSTEOGENESIS IMPERFECTA
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Objectives:
Cardiovascular abnormalities have been reported in adults with osteogenesis imperfecta (OI); however there are few studies in paediatric population. The purpose of this study was to investigate cardiovascular findings by echocardiography in children with OI.

Methods:
A prospective study of forty-three patients typed according to modified phenotypical Sillence classification. Aortic and left ventricular diameters were measured by echocardiography, including 2D and doppler.

Results:
43 patients (51,2% Males and 48,8% Females) with OI types I (n=20), II (n=1) III (n=5), IV (n=12), V (n=3) and VI (n=2). Left ventricular measures were: left ventricular end diastolic (LVIDd) 38 ± 7.1 mm, interventricular septal diastolic (IVSd) 6.1 ± 1.6 mm, left ventricular posterior wall thickness in diastole (LVPWd) 6 ± 1.5 mm. Right ventricular end diastolic 19.3 ± 5.1 mm. Aortic diameters were: Aortic annulus (AoAn)15.4 ± 3.2 mm, sinus Valsalva (SV) 20.5 ± 4.3 mm, sinotubular junction (STJ) 17 ± 3.6 mm, Ascending Aorta (AscAo) 17.8 ± 4.6 mm and Descending aorta (DescAo) 11.1 ± 2.9 mm.

Significant differences were found between dimensions of descending aorta among patients with OI by mutation in COL1A1 and COL1A2. DescAo (mm): 10.01 vs 13.1, p<0.05. DescAo (Z-score): -0.4 vs 0.2, p<0.05. When analysing the clinical characteristics of each genetic subgroup, only significant differences were found in BMI (p50 19.99 Kg/m2 vs 20.47 Kg/m2) and blue sclera (27% in COL1A2 vs 80% in COL1A1). As expected, there were higher wall thicknesses to a higher degree of BMI.

Conclusions:
Aortic dilatation was the most frequent finding. In our study, the descending aorta diameter was significantly higher in patients with OI by mutation in COL1A2 compared to COL1A1. In COL1A2 group, BMI values were significantly higher. These results indicate the need for early structural and functional echocardiographic assessment and the follow-up starting at the diagnosis.

P14
The importance of dental screening in children with Osteogenesis Imperfecta
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Introduction:
Dentinogenesis Imperfecta (DI) can be associated with Osteogenesis Imperfecta (OI), otherwise known as DI type I, which can significantly increase the burden of care in children. DI can also affect teeth only (DI Type I & III). The OI clinic at Great Ormond Street Hospital (GOSH) has a long
established link with the Eastman Dental Hospital (EDH) for dental screening of OI patients, and has audited this service since September 2011, via the anomalies clinic.

Results:
Of the 418 patients audited on the anomalies clinic, 8% had OI without DI, 5% had OI & DI (DI type I) and 5% had DI only (DI type II), with no skeletal abnormalities. Patients with OI only also presented with Molar Incisor Hypomineralisation (MIH), hypodontia and microdontia. The majority of cases with OI & DI (DI type I) were OI type III. All patients with OI & DI (DI Type I) required specialist Paediatric Dental management. The dental team have also highlighted atypical features of DI (diagnosed as DI Type III) in a pair of siblings with clinical features of OI (femoral bowing and fractures), with no known gene identified. DI type III has never been reported in association with OI, and suggests a new gene mutation.

Conclusion:
Dental screening for patients with OI is essential, to ensure the appropriate care is provided by specialist services if required. Other dental anomalies may be present, as well as the potential to identify new gene mutations with the appropriate dental phenotypic information.

P15
Changes in scleral colour and perceptions of fracture risk in children and young people with osteogenesis imperfecta
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Objectives:
There are few published data about beliefs regarding scleral colour and fracture risk in OI. We sought to understand such beliefs and whether they led to any restriction of activity.

Method:
Eligible subjects (0-25 years with OI and blue or grey-coloured sclerae) were identified. A questionnaire collected data from parents and children about demographics, variability in scleral colour (frequency and duration of scleral darkening), beliefs regarding association of scleral darkening with fracture risk and whether behaviour was modified according to changes in scleral colour. Pearson’s Chi squared and/or Fisher’s exact test statistics were used to compare proportions.

Results:
Mean age was 9.2 years (1.8-17.6 years). 18/33 had type 1 OI. 21/33 described periodic darkening in scleral colour. Median reported frequency of episodes was 2.5 months with 9/12 giving a frequency of between 2 and 4 months. 14/15 described duration of episodes in terms of days. 11/21 described scleral darkening in relation to fractures. 14/21 believed in an ongoing association between fluctuations in scleral colour and fracture risk.

13/18 with type 1 OI described periodic darkening in scleral colour compared to 8/15 with more severe OI (p=0.26). 9/13 had limited the activity of their children to some degree during periods of darkening in scleral colour compared to 3/8 with more severe OI (p=0.20). 5/9 were still limiting the activity of their children (mean age 12.5 years; range 6.0-17.6 years).

Conclusion:
In children with OI, 21/33 described fluctuation in scleral colour, the duration and frequency of which was remarkably consistent. The belief in an association between scleral colour and fracture is common. Correspondingly, many children are subject to restrictions in their activities during periods of scleral darkening.

Take home message:
Restriction of activity during scleral darkening is common despite a lack of evidence to support such action.
P16
Aortic dissection and Osteogenesis imperfecta: a rare but devastating association

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Objectives
The association between Osteogenesis imperfecta (OI) and cardiovascular abnormalities has been known for years. But the incidence and characteristic of cardiovascular abnormalities in OI patients are not well understood. OI-related valvular insufficiencies and aortic dilatation have been well documented, however, reports of aortic dissection in the setting of OI remains rare. There are only six documented cases of OI-related aortic dissection in literature, which are all in men.

Method
Patients were evaluated in OI-Genetics clinic with appropriate history, examination and targeted OI exome panel testing. Existing literature on OI-related cardiovascular problems was reviewed.

Results
We present two patients with clinical diagnosis of type 1 OI, first patient is a 42-year old woman with history of multiple low trauma fractures who has had OI-related aortic dissection which was successfully repaired. This is the first reported female with OI-related aortic dissection. All the previously reported cases were male. Genetic analyses so far have proven negative. Second patient is a 48-year old woman with a molecular diagnosis of OI (pathogenic deletion c.614del in exon 8 of COL1A1) with a family history of OI-related aortic dissection in her father. The aim of this case report is to add to the scarce existing literature regarding OI-related aortic dissection.

Conclusion
In total, there are now eight documented cases of OI-related aortic dissection in literature. Obtaining more evidence will improve our understanding of the risks of cardiovascular abnormalities in OI patient and help develop criteria for screening and management.

Take home message
Aortic dissection is a rare complication of OI with fatal consequences if not treated promptly. This report adds to the evidence of cardiovascular risks in OI and the need for careful cardiac surveillance in patients with even mild forms of OI.

P17
Health assessment of osteogenesis imperfecta patients based on 3D non-linear diagnostics NLS

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Objectives
Functional status of skeleton, organ, brain, tissue cells and other parts was assessed in patients with osteogenesis imperfecta (OI).

Methods
Three-dimensional non-linear diagnostics (3D-NLS) of multiple systems and locations of 21 OI patients and 15 healthy people were carried out using Metatron system.

Results
In motion system, significant differential interval distribution of loss compensation was observed in long bones of the humerus, ulna, femur and tibia; joints of elbow, wrist, hip, knee and ankle; the vertebrae of cervical vertebra, lumbar and thoracic bodies between OI and healthy people. The percentage of decompensated interval distribution of long bone and joint together was 80. The percentage of 39.13% and 78.26% was observed in the distribution of connective tissue and cartilage cells in OI patients with decompensated interval distribution, respectively. In the auditory system, the decompensated interval distribution of the left temporal lobe of the left temporal lobe in OI

62
patients was 17.39%, while no distribution was recorded in the healthy people. In the respiratory system, lost compensatory interval of left and right lobe in the respiratory system accounted for 9% and 17% respectively. The percentage of 65% and 86.96% in loss compensation distribution was showed on the left side of the lung and the right side of the hilar area in OI patients. The loss compensation distribution of 4.35%, 4.35%, 8.70%, 17.39% and 26.09% was identified in the heart, urinary system left kidney, right kidney, digestive system.

Conclusion
OI was found abnormality in the sports system, connective tissue, the auditory system, respiratory system, circulatory system, urinary and digestive system and other aspects according to 3D-NLS, which is highly in accordance with the literature report.

«Take home message»
The study provides the foundation for the healthy evaluation and monitoring of OI patients.

P18
CLINICAL CHARACTERISTICS OF OSTEOGENESIS IMPERFECTA AND COLLAGEN TYPE I GENES.
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Objective:
The aim of this study was to associate the clinical characteristics of Osteogenesis Imperfecta with mutations in COL1A1 and COL1A2.

Methods:
OI types I, III or IV were enrolled. Clinical findings were recorded. COL1A1 and COL1A2 were analyzed by Ion Torrent PGM. Data were processed using Torrent Suite and Ion Reporter. Mutations were classified as haploinsufficiency (quantitative protein defect) and helical glycine mutations (qualitative protein defect).

Results:
In total 48 individuals (male=19) were included, 32 cases with mutations in COL1A1 and 16 cases in COL1A2. Quantitative defect was found in 19 individuals, 17 (89.5%) in COL1A1 and 2 (10.5%) in COL1A2. 15 were diagnosed with OI type I and 4 with OI type IV. Qualitative mutations were identified in 22 cases (11 in COL1A1 and 11 in COL1A2). All 7 OI type III were identified with qualitative mutations (4 in COL1A1 and 3 in COL1A2). Quantitative defects were associated with OI type I whereas qualitative defects with OI type IV (p=0.003). Qualitative mutations showed a tendency to lower height z-score comparing to quantitative mutations (-4.95[SD=2.72] vs. -2.74[SD=4.77] p=0.05). Haploinsufficiency mutations in COL1A1 was associated with positive family history (p=0.015), whereas dentinogenesis imperfecta was associated with helical glycine mutations in COL1A1 (p<0.001). No association was observed between the mutations and blue sclera.

Conclusion:
Individuals with haploinsufficiency mutation have shown a higher mean height z-score than individuals with helical glycine mutations. Quantitative protein defect was associated with OI type I and positive family history that is associated with a mild form. OI type III and IV and dentinogenesis imperfecta were associated with qualitative mutations. Individuals with Haploinsufficiency mutation have shown a tendency to higher mean height z-score than individuals with helical glycine mutations. Understanding the molecular mechanisms of OI is important for genetic counseling, prognosis and correlation to treatment options.

P19
Clinical variability of OI type V
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To evaluate clinical variability of OI, we observed 254 patients with a diagnosis of OI from the former USSR in 2006-2017. Molecular genetics testing was performed by NGS using a comprehensive connective tissue 494-gene panel or by Sanger sequencing.
8 patients were diagnosed as OI type V. In 5 patients the diagnosis was based on clinical evaluation (excessive calluses, intraosseous membrane, radial head dislocation). 3 patients initially were diagnosed as type III/IV due to lack of typical features of OI V. However, after molecular genetic testing a known hotspot mutation in IFITM5 (c.-14C>T) was found in all these cases.

In one patient with a severe OI type V excessive callus formation has been noted after surgery aimed to improve elbow joint mobility. Confirmation of OI type V modified treatment options in other patients, considering a risk of excessive calluses formation after surgical intervention.

All 8 OI type V patients showed clinical improvement after multidisciplinary treatment that included bisphosphonates, rehabilitation, psychological support and social adaptation.

Conclusion:
Though type V is a relatively rare form of OI, DNA testing is necessary for optimal choice of treatment options and adequate genetic counseling.

P20
Genotype-phenotype correlations in patients with OI from former Soviet Union
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To evaluate clinical and genetic variability of OI, frequency of recessive forms, influence of various factors on OI severity we observed 254 patients with a diagnosis of OI from the former USSR in 2006-2017. 198 children were treated by interdisciplinary team. Treatment included bisphosphonates, correction of deformities, rehabilitation and physical therapy, psychological support and social adaptation. Molecular genetics testing was performed by NGS using a comprehensive connective tissue 494-gene panel.

In 99 patients genetic testing was performed by Genomed Ltd. to identify causative mutations. 81 patients have mutations in COL1A1 and COL1A2 genes: 64 missense mutations, including 58 glycine substitutions; 16 loss-of-function mutations (nonsense, frameshift and splice site alterations) and, in one case, a whole COL1A1 gene deletion. Several mutations were found in multiple unrelated patients; all of them were described earlier as relatively frequent, which is indicative of hotspots. In one OI I patient with consanguinity, a known COL1A2 mutation (p.Gly751Ser) was found in homozygous state, indicating recessive inheritance. 32 mutations detected in collagen genes, to our knowledge, were novel. A known hotspot mutation in IFITM5 (c.-14C>T) was found in 4 cases; 10 patients have homozygous or presumably compound heterozygous mutations in SERPINF1, PLOD2, LEPRE1 and FKBP10. In 4 patients, causative mutations were not identified.

After a combined clinical and molecular genetic evaluation, the 99 patients were diagnosed as OI types I, III, IV, V, VI, VIII, XI, and Bruck syndrome. Possible genotype-phenotype correlations will be discussed. Genetic counseling has been provided to all referred families. Establishing a molecular genetic diagnosis changed clinical prognosis in cases with non-collagen mutations. Multidisciplinary approach contributed positive dynamics in bone density, activity and social adaptation.

According to our observations, physical activity and other lifestyle factors are no less important in determining severity of clinical manifestations than the underlying genetic cause.

P21
Genotype-phenotype correlation in 364 Italian patients with dominant Osteogenesis Imperfecta
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To evaluate clinical and genetic variability of OI, frequency of recessive forms, influence of various factors on OI severity we observed 364 Italian patients with a diagnosis of OI in 2006-2017. 81 children were treated by interdisciplinary team. Treatment included bisphosphonates, correction of deformities, rehabilitation and physical therapy, psychological support and social adaptation. Molecular genetics testing was performed by NGS using a comprehensive connective tissue 494-gene panel.
Objectives
To better characterize Osteogenesis Imperfecta (OI) and facilitate the follow-up management we performed a genotype-phenotype correlation study analyzing an homogeneous Italian population of 364 dominant OI patients.

Methods
All patients have been classified according to Silence criteria and they have been evaluated for scleral hue, anthropometry, DI, triangular face, BMD lumbar spine, wormian bones (WB), frontal bossing, joint hyperlaxity, hearing loss and cardiac defects. As causative genetic determinants point mutations and large rearrangements in COL1A1-A2 genes have been considered, including also those in the N- and C-propeptide. To avoid a bias age-related the same analyses have been performed both in the whole population and only in the adult group.

Results
The population study is composed by 262 patients affected by OI type I (72%), 24 by type II (6,6%), 39 by type III (10,7%) and 39 by type IV (10,7%). A total of 309 patients with COL1 mutations have been identified (230 in COL1A1 and 79 in COL1A2); no mutations were discovered in 55 patients (15,1%).

None gradient of phenotypic severity through the COL1 genes have been identified and mutations localized in clusters considered ‘lethal’ were causative of I-IV OI types. Otherwise, some new interesting correlation have been highlighted: heart problems were associated to quantitative alterations (P=0.043), the presence of DI and OI type III were related to serine substitutions in α1-chain (P=0.04), whereas OI type I to α2-Ser substitutions (P=0.007). Qualitative alterations were associated to the presence of white and gray sclera, while quantitative defects to blue sclera (P<0.0005).

Conclusion and take home message
Genotype-phenotype correlation data obtained from the biggest population-based correlation study on dominant OI patients confirmed on one side some previously identified association and pointed out, on the other, new interesting findings that could be useful to predict the phenotype and manage the follow-up.

P22
A novel COL1A1 mutation in a Japanese family with OI
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Osteogenesis imperfecta (OI) is a heterogeneous disorder caused by mutations in the genes encoding collagen, mainly COL1A1 and COL1A2. Here we identified a novel mutation in COL1A1 in members of a Japanese family clinically diagnosed with OI.

Patient 1 (P1) was an adult male reporting a normal daily life who was clinically diagnosed with OI based on a history of broken long bones more than 30 times leading to deformities of his extremities. He also had blue sclera, a short stature, and severe scoliosis. He had undergone previous mitral valve repair and aortic valve replacement. His father had no history of OI. His mother (P2), aunt, and grandfather were suspected of having OI from their history of long bone fractures, blue sclera, and short stature; they did not have scoliosis or heart disease. The apparent severity of OI in this family was increased through the grandfather to P1, and was more severe in P1 than in P2. We used next-generation gene sequencing to analyze the genetic cause of OI in P1 and P2 and detected a novel candidate mutation (c.750+2T>A) in COL1A1 of P1.

To confirm this mutation was the genetic cause of OI, direct sequencing of the mutation was performed and the same mutation was identified in P1 and P2 but not in the father. Mosaicism was also ruled out.

The severity OI of P1 was possibly the result of phenotypic penetrance causing weakening of the connective tissue of the heart, and of the ligaments and muscles supporting the spine and long bones. P1 also reported a more active life than P2, so environmental factors (e.g., exercise load) might have increased the risk of bone fracture and may have accelerated the development of valve regurgitation and scoliosis.
P23
Difficult treatment in a radial head dislocation case of Osteogenesis Imperfecta type V
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Objectives:
In this case report, we want to focus the difficulties of the correct diagnosis in Osteogenesis Imperfcta (OI) type V, describing the pitfalls that could be faced in the treatment of a radial head dislocation in this type of OI.

Methods:
A child aged 5 years old came to our clinical observation, with a positive anamnesis of multiple fractures, grey sclerae, osteoporosis and ligamentous hyperlaxity. A genetic test showed the patient had no mutations in COL1A1/COL1A2 genes. We made a clinical diagnosis of OI type I and started a neridronate therapy. Five years later, without trauma, the patient felt pain moving his right elbow. X-ray showed dislocation of the radial head. Was performed a surgical partial capitellectomy with lateral capsuloplasty. Three months later, the child felt pain moving the elbow. Another X-ray showed heterotopic ossifications in correspondence to the radial head and the interosseus membrane. We decided to perform a second genetic test and an osteotomy of the radial head, neck and metaphysis. Results: A pharmacological therapy was prescribed (etoricoxib) to prevent the new heterotopic ossifications formation. The patient enhanced his joint motion. The second genetic test gave the diagnosis of OI type V. Elbow motion and function improved with the pharmacological therapy. The subsequent X-rays showed the bilateral radial head dislocation, with interosseous membrane ossifications.

Conclusion:
Specific patterns in OI type V are the interosseous membranes calcifications and the trend to develop hyperplastic bone callus. The choice to treat heterotopic ossifications using etoricoxib is confirmed by literature.

Take home message:
In OI type V the surgical treatment on elbow or forearm does not seem to be an effective choice, because interosseous membrane calcification can cause recurring problems. It is mandatory to define a certain genetic diagnosis in patients showing an OI type I-like phenotype, presenting though elbow anomalies.

P24
A moderate form of OI caused by compound heterozygous LEPRE1 mutations
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Objectives.
A description of the LEPRE 1 mutations causing a moderate form of Osteogenesis Imperfecta (OI).

Methods
Review of literature about recessive LEPRE1 mutation of OI and a patient record from our OI Clinic.

Results
OI is a genetic disorder causing skeletal fragility, multiple fractures, osteoporosis and other extraskeletal manifestations. Most cases are due to mutations in COL1A1 or COL1A2. Recent investigations have discovered several other autosomal recessive genes responsible for OI. Among these genes is LEPRE1, which is involved in
post-translational modifications of the collagen. To date, more than 20 LEPRE1 mutations have been described. This mutation is carried by 1.5 % of West Africans and 0.4% of African Americans, and is associated with the VIII type of Sillence classification.

Severe or lethal presentation, progressive deformities, lack of blue sclera and dentinogenesis imperfecta, rhizomelia, wormian bones, enlarged fontanelles, kyphoscoliosis and popcorn (boulbous) appearance of metaphyses are the typical clinical manifestation of Type VIII OI.

We describe a 4 year old male with a moderate form of OI and compound heterozygous LEPRE1 mutations. (c.1080+1G>T; c.1646T>G, Met549Arg). Patient received Pamidronate at age of seven weeks of life until the DEXA score improved (normal for his age). Presented anterolateral bowing of the femurs. We observed in radiographs with intervals of 10 months, decrease of bowing.

Conclusion
Type VIII OI typically causes a severe to lethal phenotype presenting at birth with severe osteopenia, congenital fractures and other clinical manifestations. Only a few individuals have survived to childhood. This case description serves to expand the clinical phenotyping of this recessive form of OI into the more moderate spectrum.

Take Home Message
With diagnosis and early treatment, it is possible to reduce the severity of OI clinical presentation in patients with LEPRE1 mutation.

P25
WHOLE-EXOME SEQUENCING AS A POWERFUL TOOL TO UNRAVEL THE MOLECULAR PATHOGENESIS OF OSTEGENESIS IMPERFECTA
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OBJECTIVES
Osteogenesis imperfecta (OI) comprises a heterogeneous group of disorders characterized by bone deformities, low bone mass, brittle bones, and connective tissue manifestations. Dominant mutations in the COL1A1 or COL1A2 genes account for more than 80% of the cases, whereas recessive defects can be found in a plethora of genes. In a small subset of patients, the genetic basis remains elusive, suggesting the involvement of other, yet to be discovered, genes. The aim of our study is to identify the causal defect in molecularly unexplained patients, phenotypically suggestive for OI.

METHODS
Nineteen COL1A1/COL1A2 negative OI-like cases were selected for whole-exome sequencing (WES) based on clinical severity and positive familial anamnesis. Mapping and data analysis were performed using commercial (CLC workbench) and in house developed tools. Variant prioritization was based on literature and the Ingenuity Variant Analysis software. Sanger sequencing was used for variant confirmation and segregation analysis.

RESULTS
Hitherto, causal mutations were identified in four cases. In a first proband, a homozygous missense mutation was found in the know OI-gene LEPRE1 (c.446T>G, p.(Leu149Arg)), encoding prolyl-3-hydroxylase-1. The second proband harbored a homozygous missense mutation (c.1444C>A, p.(His482Asn)) in the hypophosphatasia-linked ALPL gene. In a third consanguineous family a homozygous nonsense mutation was detected in the osteopetrosis-associated gene CTSK (c.721C>T, p.(Arg241*)). A fourth proband carried a causal heterozygous missense variant in PIEZO2 (c.8057G>A, p.(Arg2686His)), a gene which
associates with arthrogryposis. Data analysis for the other families is ongoing.

CONCLUSION/TAKE HOME MESSAGES
In 21% (4/19) of the patients mutations were identified in the LEPRE1, ALPL, CTSK and PIEZO2 genes. Our findings illustrate that WES is a valuable tool for the detection of mutations in known OI genes, but also that opening up the WES data allows us to identify causal defects in genes associated with phenotypically overlapping disorders.

P26
Interaction analysis of non-coding RNAs and target genes for Wnt1’s ten miRNAs
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Objectives:
Interaction analysis of Wnt1’s target miRNAs and their corresponding circRNAs, lincRNAs and target genes. Screening of circRNA molecules that function as a sponge in the miRNA of the target Wnt1, and then study their possible functions. Methods: Target miRNAs of Wnt1 was analyzed either by miRWalk predication or PubMed literature. Dual luciferase report experiment was conducted to testify the predicted miRNAs with high credibility. The corresponding CircRNAs, LincRNAs and genes of selected Wnt1’s target miRNAs were predicted by StarBase software. The relationship among CircRNAs, lincRNA, miRNA and target genes were comprehensively analyzed by Cytoscape, DAVID and GO. The miRNA sponge effect will be screened by luciferase assay. The transient expression vectors for interesting circRNAs were constructed for further functional study.

Results:
A total of eight miRNAs targeting Wnt1 including let-7e, miR-21, miR-34a, miR-122, miR-146a, miR-148a, miR-148b, and miR-152 are reported in the literature. Both miRWalk predication and our luciferase assay support that miR130a and miR130b are the target miRNAs for Wnt1. The network relationship were drew among these ten different miRNAs and their corresponding circRNAs, lincRNAs and target genes, which covers focal adhesion, Notch, TGF-beta, MAPK and other signaling pathways. Hsa_circ_001421 was found to interact with miR-34a, miR-130a, miR-130b, miR-148b, miR-152, LINC00667, and INHBB gene, Hsa_circ_000601 interacted with miR-34a, miR-148a, miR-148b, miR-152 and TGIF2 gene in TGF-beta signaling pathway.

Conclusion:
MiR-130a/b was proven to be the targets of Wnt1. The further identification of target miRNAs of hsa_circ_001421 and hsa_circ_000601 will be performed by luciferase screening. Over expressing and inhibition of these two circRNAs will be for the future functional study.

«Take home message»
Wnt1’s target miRNAs and their interaction with circRNA are disclosed and further circRNA’s function are going on study.

P27
Novel mutation in SERPINF1 causing Osteogenesis Imperfecta type VI
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Objectives and Methods: Osteogenesis Imperfecta (OI) type VI is a rare recessive disease caused by SERPINF1 mutations. OI type VI patients are reported to be normal at birth with normal teeth
and sclerae. Long bone fractures and deformities occur between 6 and 18 months of age. Diagnosis can be challenging as clinical evidence alone may be insufficient. Here, we report a 2-year old boy who presented with long bone fractures suspected to be physical abuse with removal of parents’ custodial rights.

Results:
The patient was born at term to healthy unrelated parents following an uncomplicated pregnancy. He had normal gross motor skills and started walking at 12 months. His first fracture (clavicle) occurred aged 1.1 years. Femur, fibula, pars of C2 vertebra and multiple rib fractures had occurred by 2.4 years following several episodes of minor trauma. He had off-white sclerae, ligamentous laxity and was relatively tall (91st percentile).

He had normal bone biochemistry (including 25OH-vitamin D). Skeletal survey undertaken at presentation did not provide any clear indication of underlying bone disease. Targeted gene panel testing was undertaken. He was compound heterozygous for a c.582_585dup, p.(Thr196Valfs*8) likely pathogenic variant and a c.272C>A, p.(Ala91Asp) variant of uncertain significance in SERPINF1. Deeper phenotyping, including bone biopsy showing ‘fish scale’ appearance, confirmed type VI OI. He developed L5-S1 spondylolisthesis and unequivocal vertebral wedging by 2.5 years. He was started on zoledronic acid aged 2.5 years.

Conclusion:
Compound heterozygous variants c.582_585dup,p.(Thr196Valfs*8) and c.272C>A,p.(Ala91Asp) in SERPINF1 are novel. OI type VI in the absence of extraskeletal features can present as a diagnostic challenge.

Take home message:
Careful consideration should be given to genetic tests when fracture history is strongly suggestive of bone fragility even in the absence of other clinical and radiographic features of OI.

P28
Surgical treatment of Osteogenesis Imperfecta in a Developing Country with Resource Limitation: Results of Rodding and Impact on Ambulation and Refracture.
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Introduction:
Delay in presentation and surgical intervention is not unusual in the developing world as regards treatment of OI due to various local and cultural beliefs. Most children are treated with plasters, bone plating and K wire fixation until the initial fractures heals only to be followed by a refracture. The greatest myth in treating children with OI is that most parents are counselled that “plaster treatment is sufficient” for fracture healing. The purpose of our study is to review the results of 21 children with OI cases who have been treated with sub-optimal fixation or those that have been allowed to refracture with progressive increase in deformity.

Patient and Methods:
We reviewed treatment of 21 OI patients that presented at various age groups for treatment of recurrent fractures. Six children had undergone two or more surgical procedures for their fractures before referral. 28 femur and 21 tibia were rodded using a combination of Rush Rods, local Fassier Duval Rod, K wire and supplementary plating was done in 5 children (8 femur) to achieve stability. Three children in the group (5 humerus) also underwent Humeral rodding. Ambulatory status was assessed by the Hoffers and Bullock grading and muscle power was recorded using the MRC grade. Ten children had received intravenous bisphosphonates pre-operatively. Post-operatively the children were assessed for ambulatory status, pain, and ability for independent self-care.

Results:
The mean follow-up period was 34 months (24 – 48 months). Rush rods were used in 20 femurs, Fassier Duval (FD) rod in 6 Femur and in two cases with narrow intra-medullary canals “K” wires were used. For the tibia, 15 children received rush rods
and in 6 cases a FD rod was used. The mean time to fracture union was 8 weeks (6 weeks – 12 weeks). Before surgery, 13 children were in Hoffer grade 4 (Wheel Chair independent or carried by parents in the developing country), four were able to ambulate with walking aid (Hoffer grade 3b), and 4 were able to walk about in the house without aids (Hoffer grade 2). After the rodding procedure the ambulatory status changed in 50% of children – seven children (33%) became physiologic walkers (grade 3b), three could walk unaided with orthosis (grade 1b) and one child with mild OI could walk unaided (grade 1a). No child had deterioration in ambulatory status. The incidence of new fractures reduced dramatically after rodding. Only two children had re-fractures at the distal end of the rod due to growth of bones. Supplementary plate fixation was done in six cases. No case of nonunion was seen but three children had asymptomatic incomplete union of their femur os teotomy. One incomplete union was see with the humerus fixation. The mobility status and ability to function had improved in children at the latest follow-up.

CONCLUSIONS:
Intramedullary rodding treatment for recurrent fractures in children with OI improves their mobility potential and prevents repeated cast application which is not only cumbersome for the children and families but also causes further osteopenia and deterioration in the quality of bone. Despite only 50% improvement in ambulation, parents reported satisfactory outcome as the re-fracture rate reduced to almost nil. Many parents had not been told that rodding is an option for treatment for repeat fractures as reflected in the higher mean age of surgery in this study. Increase awareness amongst doctors and caregivers is required to advocate early rodding for children with OI to prevent recurrent fractures.

P29
Preoperative halo traction with posterior spinal release and pedicle screws fixation for the treatment of OI with severe scoliosis
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BACKGROUND:
Scoliosis is common in patients with osteogenesis imperfecta especially those with severe bone fragility. With improvement of the preoperative management and fixation and fusion techniques, the scoliosis in OI can now be better corrected. But to the best of our knowledge, there are only rare prospective studies on OI patients who have a rigid curve more than 80° and flexibility less than 35%.

METHODS:
6 OI scoliosis patients were recruited from September 2013 to June 2016. All patients had rigid curves and underwent spinal correction. CT brain was performed to determine the position of the screw fixation for the halo traction. Halo-traction starting with 5% of body weight and 1% weight added everyday until 30-40% of body weight weight followed by posterior release and posterior spinal fusion using pedicle screw system. X-rays evaluating the Cobb’s angle, listing, truncal shift, percentage of correction were performed. Scoliosis research society-22 questionnaire (SRS-22) scores were performed pre- and post-traction and pre-and post-operation and during follow-up visits. The operation time, blood loss, hospital days, and hospital charges were accounted.

RESULTS:
These patients were followed up for an average of 18 months (range, 12 - 36 months). The average age was 14.8 years old. No serious complications were observed. One patient had poor tolerance of halo traction and the traction was stopped prematurely. One could not tolerate the traction beyond 25% of the body weight. Long spinal fusions were used to correct the deformity. Tranexamic acid and cell savers were used intra-operatively. The average correction of the major curves was from 104.9 degrees (112-105) to 54.4 degrees (71-47).

CONCLUSIONS:
In OI with a rigid curve and poor flexibility, slow accumulated halo traction with wide posterior spinal release can provide satisfactory correction.
Long spinal fusion is also achievable using pedicle screw system.

P30
Cutout of non-telescopic Intramedullary nail after tibial corrective osteotomy in skeletally immature patients with osteogenesis imperfecta

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Introduction
Anterior tibial bowing is relatively common in OI patients due to bone fragility, repeated fractures and strong muscle pull posteriorly. Modified Sofield operation can help straighten the bone but recurrence of the deformity and cutout of the intramedullary rods are not infrequent leading to revision surgery especially in non-telescopic nails. The aim of the study is to identify the risk factors leading to early cutout of fixation in tibia using non-telescopic nail.

Methodology
This is a retrospective review of the tibial corrective osteotomy performed between 2015-2016 with minimum follow-up of 1 year. All patients were skeletally immature, genetically typed, with retrievable medical records and x-rays. Types of OI, age, pre-operative deformity, and position of the intramedullary nail in relationship with the distal epiphysis were evaluated.

Results
A total of 16 patients (24 tibia) involving 11 males and 5 females were reviewed. The average age of patient was 7.1 (2-11). 6/24 (25%) tibia have cutout within the review period. Comparing the group with cutout of nails and the one without, the nail positioned at the anterior third of the epiphysis (p<0.009) as well as those with deformity larger than 50 degrees (p<0.001) have higher chance of nail cutout.

Conclusion
Non-telescopic nails may be associated with high chance of cutout of nails in skeletally immature patients when not positioned properly. From the present study, in tibial deformity correction, the non-telescopic nail should be placed within the middle and posterior third of the epiphyses to reduce the cutout. Furthermore, anterior bowing with deformity greater than 50 degrees should be treated with cautious with adequate bony correction to ensure proper positioning of the nails.

P31
Intramedullary Nail for Bone Fixation in Adolescents and Adults with Small and Fragile Bones. New Device.

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Objectives.
Evaluate the results with the GAP nail (combined Intramedullary/Extramedullary implants) in patients with short stature and bones with small diameter and short longitude.

Describe the stability of the fixation of fractures or osteotomies in bones with small diameter and closed physis in base of radiological images.

Methods
21 patients with these conditions had surgery with this system. In total, 26 long bones: 18 femurs and 8 tibias. The age range was 8 to 16 years old. Three patients suffer from Osteogenesis Imperfecta (OI): 11 patients with type IV and 8 type III of Silence Classification. 1 patient with McCune-Albright syndrome, and 1 more Cerebral Palsy (CP) case with quadriplegic pattern.

Results
2 patients with OI type IV were treated as emergencies due to femoral fractures; 1 of them had fractures on both femurs. One 14 year-old girl with fibrous dysplasia of the femur and 1 patient of 16 years old with quadriplegic pattern had a severe deformity of the proximal femur, which is sequel of previous surgeries. The nail’s smallest diameter was 4.8 mm and the biggest was 6.4 mm; the longitude ranged from 200 mm to 320 mm. All nails were locked proximally and distally. The consolidation was evaluated with radiographs, and observed at 8 to 12 weeks.
Conclusion
In all the cases, we achieved a stable system with this implant in these extremely fragile bones with diameters below the conventional parameters. It was not necessary to use a brace, cast, or splint in the limbs in the postoperative period.

Take Home Message
The GAP Nail is a useful implant to fix fractures or correct deformities in patients with short stature, bones with small diameter and longitude, and closed physes.

P32
Locally Manufactured Telescopic Rods in Treatment of Osteogenesis Imperfecta Cost Effective Approach for Developing Country
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Objective:
The purpose of this study was to find out implant safety and quality of life in terms of ambulation and socialization.

METHODOLOGY:
This descriptive case series was conducted at Paediatric Surgical, NICH Karachi, Pakistan over a period of two years from 2013 to 2015. Material used was locally manufactured telescopic rods made of internationally specified medical grade steel. Standard technique as described by Sofield-Miller was used. All patients were also receiving biphosphonates. Patients were kept in hospital overnight and then followed up in Outpatient at regular intervals. Clinical and radiological evaluation was done. Ambulatory status were also analyzed. Minimum follow up was of three months and maximum of twelve months. Descriptive statistics were used like frequencies and numbers to present data.

Results:
Total number of patients operated was twelve. A total of 19 long bones were operated in these patients. All patients had moderate and severe form of OI with history of multiple fractures. There were 7 males and five females. The age ranged from 4 year to 14 year with mean age of 8.5 year. This included eight femora and eleven tibia. Number of femora operated was 08 and tibia in 11 patients. There was no early complication in all the patients and hospital stay was 24 to 48 hours. Pain was the only complaint in early period. Other complications found were migration of rod in three patients, fracture post trauma in one patient and bending of rod in one patient. All of these complication were already been described internationally.The cost of the locally manufactures rod is approximately 90 US dollars.

Conclusion:
The ambulatory status improved after the telescopic rods surgeries, especially when it was associated with intravenous administration of biphosphonates. Locally manufactured rods are as effective as international rods. There is a huge cost saving.

P33
Initial experiences with the combined endo-exomedullary GAP nail for the treatment of femoral fractures in Osteogenesis imperfecta
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Objectives
Surgical treatment of fractures in patients with osteogenesis imperfecta(OI) is often a surgical challenge due to fragility and deformities of the bones. The combined endo-exomedullary GAP nail from Pega Medical has recently been introduced as an implant for treatment of femur fracture and deformities in OI. We present two cases of femoral fractures in OI type IV patients treated with the GAP nail.

Methods/ Results
Case 1:
At a routine visit at the endocrinologist this 26 yr old woman complained of thigh pain. Radiography revealed a crack of the lateral cortex located in the subtrochanteric region of the right femur. For the preop planning long standing pictures of the lower extremities were taken and showed coxae vara, femoral varus and severe genu valgum. The program Bone Ninja was used to plan osteotomy levels. A week before planned surgery the patient had a complete fracture at the site and we decided for antegrad nailing with the GAP nail. To avoid further valgus deformity at the right knee, axial correction was made in the distal osteotomy using blocking screws according to the pre-operative plan.

Case 2:
A 40 yr old female suffered from a displaced fracture of the hip. Radiography showed a varus of the left femur and collum. The fracture was treated with antegrad GAP nail in femur using the two lack screws in the system for fixation of the fracture. Two level osteotomies were done to correct the varus deformity.

Conclusions
The combined intra- and exomedullary support of the GAP nail provided good stability in the two cases. The long standing X-rays in the first case made detailed preoperative planning possible and could be recommended as part of routine follow up in OI type IV.

Take home message
Case 1 demonstrates the importance of an interdisciplinary setup in OI.

P34
To treat the lower limb deformity in adult patients with osteogenesis imperfecta
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Objective:
To evaluate the safety, therapeutic effect and complications of the operation on lower limb deformity in adult patients with osteogenesis imperfecta.

Method:
22 adult patients(male,13; female,9) with osteogenesis imperfecta were treated from August, 2009 to August, 2015. Of all the patient, the number of type III is 5, type IV is 15, type V is 2. The age ranged from 15 years and 1 month to 43 years and 7 months, with average age of 23 years and 3 months. In the cases with leg length discrepancy(LLD) <2 cm, intramedullary pin fixation were used combined with plate or external fixaor in 8 cases; in cases with LLD >2 cm, 9 cases were fixed with intramedullary pins as well as external fixator and bone lengthening were performed 7-10 days after the surgery. The external fixator was applied first to lengthen the contracted soft tissues and correct the deformity and finally fixed with intramedullary pins in another 5 patients.

Results: All patients were followed up with an average of 38 months(13-64 months), and the patient’s self-care and motion ability improved greatly. The new bone consolidated well.

Conclusion: The operation of multiple osteotomy and intramedullary fixation is an effective therapeutic method for adult with osteogenesis imperfecta. Bone lengthening can be accomplished with external fixator in these patients.

«Take home message»
Although difficult and complicated, the lower limb deformity in adult patients with OI can be treated effectively.

P35
Do Femoral Fractures in adult Osteogenesis Imperfecta resemble Atypical Femoral Fractures?
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Objectives
Atypical femoral fractures (AFF) are low energy femoral fractures with characteristic radiological features and a suspected relation to bisphosphonate (BP) treatment (Shane et al. JBMR, 2013). In osteogenesis imperfecta (OI) BPs are currently the drug of choice when medical treatment is necessary. OI is characterized by skeletal fragility and pronounced bone deformity. Due to bone deformities, the radiologic appearance of femoral fractures may be different in patients with OI. Thus, we speculated whether femoral fractures in adult OI resemble AFF.

Methods
We investigated the prevalence of femoral fractures in adult patients with confirmed OI. We collected information on severity of OI and length of BP treatment. The fractures were compared to major and minor criteria of AFF.

Results
In a cohort of 55 patients, seven patients (13%) had suffered a femoral fracture in adult years (20yr+). One patient had OI type I, two had OI type III, three had OI type IV and one had OI type V. All fractures were associated with no or minimal trauma, were complete and non-committed. Five patients had fractures with a transverse configuration, located distal to the small trochanter and fulfilled the criteria of AFF. Two patients had fractures of the femoral neck in combination with coxa vara. Two patients had not received BP treatment prior to the fracture. Four patients had severe bone deformity in the femoral region due to OI.

Conclusion
Femoral fractures in OI resemble AFF. This suggests that bone deformity and decreased bone quality rather than BPs cause fractures resembling AFF.

Take Home Message
Severe bone deformity must be recognized in the continuous follow-up of adult OI. Prophylactic intramedullary rodning and deformity correction must be considered to prevent debilitating spontaneous femoral fractures in OI.
negative telescoping, CTTN decrease the need of revision in the treatment of bone deformities in OI. Take home message: The Corkscrew-Tipped Telescopic Nail (CTTN) system is an alternative implant to correct long bone deformities and to prevent or treat fractures in osteogenesis imperfecta patients. Its novel tip design allows it to prevent joint penetration and negative telescoping. Disclosure: The authors did not receive any financial support for the mentioned study. There is not any conflict of interest regarding the study.

Keywords: osteogenesis imperfecta, telescopic nail, corkscrew tip

P37

Cozen phenomenon: Lessons learnt following a salter harris type 4 tibial plateau fracture in a patient with osteogenesis imperfecta.

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Objective:
To review the medical history of a 16 year old patient diagnosis with osteogenesis imperfecta who developed genu valgum following an oblique tibial fracture.

To raise the awareness of this complication to the international community highlighting the need to monitor patients closely following this type of fracture.

To add to the body of literature on cozen phenomenon.

Method:
Retrospective case review.

Results:
X rays show that prior to the injury the patient had a normal lower limb mechanical axes. Following the tibial fracture x-ray indicated slight lateral movement of the axes within the left lower limb however this was felt to be insignificant. The valgus deformity increased dramatically over the next 12 months, with the most significant change seen one year after the initial injury. CT of the left knee 15 months after the injury confirmed a physeal bar.

Conclusion:
The patient developed genu valgum following a fracture of the tibia. Rehabilitation of this injury was impacted by a second fracture of the distal femur occurring 5 months after the initial injury. Apart from fracture related pain the patient did not report any pain within the knee until deformity was significant, 15 months after initial injury. Though an antalgic gait was present it was initially thought to be related to lower limb weakness not alterations in lower limb alignment. The patient is currently waiting a hemiepiphysiodesis to prevent worsening of the deformity. Once growth is completed the patient will undergo corrective surgery.

Take home message:
When working with children with bone disease it is important to remember the added complications that fracture can have so as to ensure these children receive appropriate and timely care.

P38

FOLDED NAILS OR BROKEN WITH FRACTURE IN LONG BONES

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Objectives:
Review of cases of fractures of long bones of lower limbs with previous nails which were broken or bent when fracture occurred.
METHODS
We reviewed a total of 33 cases in 22 patients who required surgical treatment, nail extraction and placement of a new nail. All treated in our hospital from 2000 to April 2017.

We do not include: slowly folded nails or the bone fractures Induced for nails, or the nails that bent acutely but very little and therefore they did not require urgent surgery.

We analyze the clinical type of OI, age at the time of surgery, patient’s body mass index, fracture location and nail characteristics.

RESULTS
Patients and fractures are similar in men and women. The average age is 10.4 years. Almost 73% of the cases are femurs, 20 right and 13 left.

The 88% was bent and the 12% was broken. Almost 64% of the patients were overweight or obese. 33% were type IV versus 60% type III. In 73% of cases, at time surgery, a thicker nail was introduced.

CONCLUSIONS
Surgical treatment of fractures of long bones in children with OI is more often indicated than in healthy children. The implants of choice at this age are telescopic nails. But the disease continues in despite of the nails. These nails protect the bone. But sometimes the trauma that fractures the bone also bends or breaks the nail. Now the surgical difficulty is much bigger: both situations is technically complex to solve.

P39
Surgical treatment of femur fractures and deformities with titanium elastic nails in children with Osteogenesis Imperfecta
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Objectives
From 2012 to 2016 we treated 35 patients with Osteogenesis Imperfecta (OI). We performed 43 surgeries on femur. In our study we included 26 patients (M-20, F-6) with an average age 7±2.5 years who had surgeries on femur. The indications for surgery were: hip deformities and fractures. To correct the deformity and restore the axis we performed multiple osteotomies from mini-openings. Osteosynthesis was done with titanium elastic nails with diameter from 2.0mm to 3.5mm. In 22 cases we performed immobilization with polymer cast or splint for 1 to 6 weeks, depending on stability of fixation. 25 patients received bisphosphonates before surgery.

Methods
The follow-up period was from 1 to 5 years. Evaluation of results was based on clinical assessment and control X-rays after 6-8 weeks.

Results
In 33/43 (77%) cases fracture consolidation was achieved after 6-8 weeks. Impaired consolidation in 10/43 (23%) cases. We had 9/43(21%) cases of titanium nail migration. In 8-12 weeks after surgery, 3/43(7%) patients who were using wheelchair, started to stand and walk with additional support.

Conclusion
Surgical treatment of fractures and deformities of femur in children with OI, using titanium elastic nails, gives good and excellent results. This method allows not to injure growth plates and cartilage, provides enough stability. Patients can start rehabilitation in the early postoperative period to prevent hypodynamic osteoporosis.

«Take home message»
Using titanium elastic nails with additional temporary immobilization in polymer cast or splint is a method of choice in treatment of fractures and deformities of femur in children with OI.

P40
Spinal Deformities in Osteogenesis Imperfecta Chinese Patients – Analysis of 106 Cases
Hiu Kwong Eric Yeung, Physiotherapist
Shenzhen, China
Type III OI had higher incidence of severe scoliosis. Regular monitoring at teenage period is important. Take home message

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**P41**

Pre-operative monitoring of halo-traction for Osteogenesis Imperfecta patients with scoliosis using radiation-free 3D ultrasound Scolioscan

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Objectives
Retrospective study of Osteogenesis Imperfecta (OI) patients.

Methods
106 OI patients were studied retrospectively on spinal deformities in our centre between 2014 and 2017. Radiographic measurements were performed for subjects with suspected spinal deformity (scoliometer examination ≥ 5 ATR).

Results
106 OI patients were analyzed. One of them was type II and died soon after birth. Of the 105 cases, there were 67 male (63.8%) and 38 female (36.2%) subjects. Average age was 8.3 +/- 6.1 and body height was 108.3 +/- 22.8cm. According to Sillence classification and literature, 53 of them are type IV, 26 type III, 14 type I and 12 type V.

62 subjects had spinal radiographs. Rest of them did not have obvious sign for spinal curvature and therefore no radiograph was taken. 28 (26.7%) out of the 105 subjects had scoliosis (Cobb >10°) with reducing incidence in the following order: type III (11.4%) > IV (7.6%) and V (7.6%) > I (no scoliosis). Among different types of OI, the incidence of scoliosis is different. Type V OI had the highest incidence (66.7%) to have scoliosis. The incidences for type III and IV were 46.2% and 15.1% respectively. Among the subjects with scoliosis, 18 (64.3%) had a long C curve, 10 (35.7%) had a double-curve. Type III OI had the highest incidence of having severe scoliosis (Cobb>50°). For all subjects with Cobb >25°, 3% of them developed before the age of 5, 8.8% developed between 5 and 15, 66.7% developed after 15. 72 subjects had bone density measurement and 22 of them had scoliosis. 14 (63.6%) of them had a z-score < -3. Type III subjects had a lower incidence of scoliosis if they had history of physical therapy.

Conclusion
Regular monitoring at teenage period is important.

Take home message
Type III OI had higher incidence of severe scoliosis.
of the thoracic curve measured 79.4' without traction. At 8.5kg, the angle reduced to 65.4'. When traction increased to 11kg, the angle was 66.3'. Further reduction of Scolioscan angle was noted with higher poundage of traction. The angle was 58.4' at 13.5kg traction and 51.3' at 15kg. Net reduction of Scolioscan angle was 28.1'.

Conclusion
Halo-traction reduces scoliosis curvature in OI.

Take home message
Halo-traction can be a pre-operative procedure for OI scoliosis.

P42
Femoral rodding with Fassier-Duval telescopic nail. Intraoperative bleeding in patients with Osteogenesis Imperfecta type III: observations, risk factor analysis and hypothesis of prevention
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Objetives:
In orthopaedic surgery of Osteogenesis Imperfecta (OI), the intraoperative bleeding is an important problem to deal with. Aim of our study is to identify predictive risk factors about intraoperative bleeding, in patients affected by OI type III.

Methods:
Has been managed a retrospective analysis on 23 patients (6-13 years old), treated to correct femoral deformities or to perform femoral shaft fractures osteosynthesis, using Fassier-Duval telescopic nail (FD). In order to obtain an estimate of the surgical bleeding, one must resort to a calculation based on an algorithm, which evaluates the ratio between the effective blood loss divided by the total blood volume expected per age and weight (Gamma distribution).

Results:
The average blood loss was 237.4 ml (0.12 Gamma). In 7 of the cases it was necessary to perform postoperative transfusions. Patients less than 10 years old had a minor bleeding. A higher number of osteotomies was associated to a significantly increase bleeding. Patients who were never treated with bisphosphonates, showed a significantly higher bleeding rate.

Conclusion:
Patients affected by OI type III have a high risk of severe surgical bleeding, even caused by the platelet dysfunction. Moreover, in patients never treated with bisphosphonates, the bleeding was higher. The effects of bisphosphonates on the bone could reduce the spongy bone amount and the bleeding. Bisphosphonates could lead to an alteration in coagulation cascade, inhibiting the FPPS enzyme and reducing the prenylation of many plasma proteins, including the MTHFR enzyme.

Take home message:
The correlation found with the intake of bisphosphonates, which influences coagulation, requires further prospective studies, as research to the MTHFR enzyme mutation in patients with OI type III undergoing surgical procedures. The number of osteotomies, the patient’s age and the intake of bisphosphonates for at least one year, seem to be the best predictive factors for bleeding.

P43
Olecranon fractures in children with Osteogenesis Imperfecta type I: outcomes and pitfalls.
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References:

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Objectives:
Objective of this study is to compare the results of two techniques, Tension Band Wiring (TBW) and fixation with screws, in olecranon fractures of children with Osteogenesis Imperfecta (OI) type I.

Methods:
21 olecranon fractures in 18 children with OI (average: 12 years old) were treated surgically: 10 cases were treated with screw fixation, 11 with TBW. 65% of olecranon fractures occurred as a result of a spontaneous avulsion, during the triceps muscle contraction. The follow-up was 36 months.

Results:
Among the children treated with screw, 5 needed surgical revision with TBW due to an implant mobilization. In this group, the satisfactory results were 50%. In patients treated with TBW the satisfactory results were 100%. The average Z-score, the last one recorded in the patients before the trauma, was -2.53 in patients treated with screw fixation and -2.04 in those treated with TBW.

Conclusion:
TBW represents the safest surgical treatment for patients suffering from OI type I, as it helps to prevent the rigidity of the elbow through an earlier recovery of motion, and there was no loosening of the implant. With this treatment, it is unlikely for the physis to be injured. Because of the risk of local skin irritations, the removal of the TBW is recommended, although early removal can lead to a refracture. In analyzing the average Z-score before any fracture, the fixation with screws has an increased risk of failure in combination with low bone mineral density.

Take home message:
The safest treatment for fractures of the olecranon in children with OI type I appears to be the fixation with TBW, because it showed the best results in terms of joint function recovery time, with a lower incidence of complications and pain, which allowed patients to have a significant recovery of their quality of life.

P44
Treatment of tibial deformities with the Fassier Duval telescopic nail and minimally invasive percutaneous osteotomies in patients with Osteogenesis Imperfecta type III
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Objectives:
Objective of our study is to describe the minimally invasive osteotomies technique to correct the tibial deformities in OI type III patients, using the Fassier Duval (FD) intramedullary nailing, which is considered the gold standard in this surgery.

Methods:
We analyzed the results obtained from 14 patients with OI type III, treated for tibial deformities with the mini-invasive osteotomy technique and osteosynthesis with the FD telescopic nail. The results were compared to that of a control group: 18 patients with OI type III, treated for tibial deformities with open technique osteotomies and osteosynthesis with FD telescopic nail. The follow-up was set at 18 months. In both groups were analyzed: duration of surgery, number of osteotomies, postoperative pain, time required for functional recovery and for bone healing. In order to evaluate the variations in quality of life, all the patients were given the PODCI questionnaire, before surgery and at the end of follow up.

Results:
In patients who underwent corrective surgery with the mini-invasive technique, the average duration of surgery was inferior, postoperative pain was significantly lower, recovery of 90° knee flexion was reached faster, as the full weight bear recovery. The PODCI questionnaire values were satisfactory in both groups.
Conclusion:
In the last decade, there have been major improvements in quality of life of patients with OI, due to advances in both clinical and surgical treatments. The treatment of deformities, using FD telescopic nails with the mini-invasive technique, allowed the reduction in postoperative pain, risk of infection and intraoperative bleeding, thus ensuring a better and faster functional recovery.

Take home message: Osteosynthesis with the FD telescopic nail, performed with the minimally invasive surgical technique, has improved the management of deformities in OI. However, the mini-invasive technique requires the maturation of three distinct learning curves by the surgeon.

P45
Treatment of correction in coxa valga deformity in patients affected by Osteogenesis Imperfecta
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Objectives:
Patients with moderate-severe Ostegenesis Imperfecta (OI) frequently have deformities in long bones shafts. In the hip joint of patients affected by OI, the cervical diaphyseal angle can deform in varus under weight bearing and muscular strength, restricting their joint motion and autonomy, even threatening the patient to have a fracture on the peak of the bone deformity. The objective of orthopaedic treatment must be to correct deformities and to prevent a sudden stress fracture.

Methods:
We describe 5 cases, which have a femoral cervical diaphyseal angle < 90°. The surgery consists of a subtrochanteric corrective osteotomy, a subsequent osteosynthesis with a telescopic Fassier-Duval (FD) intramedullary nail and a following stabilization of femoral neck, using K-wires and metaphyseal metallic cerclages. Every patient was immobilized in a unilateral long leg hip spica cast for 4 weeks after surgery and suspended therapy with bisphosphonates for 4 months after surgery. A rehabilitation program was started from each patient after cast removal.

Results:
Using Visual Analogue Scale (VAS) scoring system to assess postoperative pain, no cases in VAS score > 6 were registered. All of the patients restarted to walk with full weight bearing since 6th postoperative week. In 2 cases a post-traumatic femoral metallic cerclage mobilization was registered.

Conclusion:
The most interesting aspect of the surgical technique described is the possibility to correct important varus deformities of proximal femur, in pediatric patients having a severe congenital osteoporosis, by virtue of the physeal safeguard.

Take home message:
The surgical technique performed seems to be a satisfactory alternative to correct the coxa vara femoral deformity, in pediatric patients affected by OI, because it allows a good correction in cervical diaphyseal angle, protecting the physis and permitting to maintain a support in femoral shaft through the telescopic FD intramedullary nailing.

P46
Realignment and Intramedullary Rodding of the Humerus and Forearm in Children with Osteogenesis Imperfecta: Revision Rate and Effect on Fracture Rate
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Background
Intramedullary rodding is indicated for the long bone segments of patients with osteogenesis imperfecta (OI) to manage deformity and treat recurrent fractures. Historically, the focus of long bone surgery for children with OI has been the lower extremity. The purpose of this study is to report on our experience of intramedullary rodding of the humerus and forearm in children with OI and its impact on fracture rates.

Methods
This is a retrospective chart review of all OI patients who have undergone realignment and intramedullary rodding of the humerus or forearm at our institution from October 1994-February 2016. Patient demographics, surgical information, surgical revisions, preoperative and postoperative fracture rates were gathered.

Results
45 long bone upper extremity segments (26 humeri and 19 forearms including the radius, ulna or both bones) were rodded at an average age of 8.7 years (range 3.1-19.2 years). Fifteen (33.3%) of the bone segments required return to the operating room at an average of 30.8 months (range 1-90 months) postoperatively. Fracture data was available for 24 of the long bone segments. The average number of preoperative and postoperative fractures for each segment that underwent realignment and rodding was 3.58 (SD 2.84) and 0.46 (SD 0.72) respectively. The average preoperative fracture rate was 0.87 fractures/year (SD 0.47) and the average postoperative fracture rate was 0.10 fractures/year (SD 0.16).

Conclusion
In this OI patient population, realignment and rodding of the humerus and forearm appeared to reduce the fracture rate of those upper extremity bone segments. Among our population, one third required return to the operating room and one fifth required revision to a new intramedullary implant. This data may help patients and families better understand the potential outcomes of upper extremity realignment and rodding and its effect on the rate of upper extremity fractures.

P47
Evaluation of Fracture and Osteotomy Union in the Setting of Osteogenesis Imperfecta: Reliability of the Modified Radiographic Union Score for Tibial Fractures (RUST)
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Background
Evaluation of the union of osteotomies and fractures in patients with osteogenesis imperfecta (OI) is a critical component of patient care. Studies of the OI patient population have thus far used varied criteria to evaluate bony union. The radiographic union score for tibial fractures (RUST), which was subsequently revised to the modified RUST, is an objective standardized method of evaluating fracture healing. We sought to evaluate the reliability of the modified RUST in the setting of the tibias of patients with OI.

Methods
Tibial radiographs of 30 patients with OI with fractures or osteotomies were scored by three observers on two separate occasions. Each of the four cortices was given a score (1 = no callus, 2 = callus present, 3 = bridging callus and 4 = remodeled, fracture not visible) and the modified RUST is the sum of these scores (range 4-16). The inter- and intraobserver reliabilities were evaluated using intraclass coefficients (ICC) with 95% confidence intervals.

Results
The ICC representing the interobserver reliability for the first iteration of scores was 0.926 (0.864-0.962) and for the second series was 0.915 (0.845-0.957). The ICCs representing the intraobserver reliability
for each of the three reviewers for the measurements in Series 1 and Series 2 were 0.860 (0.707-0.934), 0.994 (0.986-0.997) and 0.974 (0.946-0.988).

Conclusions
The modified RUST has excellent inter- and intraobserver reliability in the setting of OI despite challenges related to the poor quality of the bone and its dysplastic nature. The application and routine use of the modified RUST in the OI population will help standardize our evaluation of osteotomy and fracture healing.

P49
Evaluation of a four centre national OI Service using a patient reported experience and outcome measure
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Objectives:
To explore experience of services users receiving specialist multidisciplinary care across four centres within England. To compare year on year trends of patient experience and outcomes across the centres.

Methods:
A condition specific patient reported experience/outcome measure (PREM/PROM) was developed for Osteogenesis Imperfecta. Parents and young people over age 12 from four centres were invited to complete the 29 item questionnaire at routine clinic review or via post. Participation at a specific time point each year provided a snap shot of patient experience in 2015 and 2016. Questionnaires were completed anonymously then collated for analysis. Patient experience of support provided by allied health professionals is presented. Results: 208 questionnaires were received from all centres across 2 years; 92 in 2015, 116 in 2016. Young people comprised 20% of responses. Half of respondents reported the OI team had helped increase independence (58% in 2015, 51% in 2016). In 2015, 27% of respondents reported not receiving help with independence (but needed) compared with less than 1% in 2016. Half of respondents reported receiving advice about taking part in PE and exercise (54% in 2015, 55% in 2016). Advice was not received by 10% of respondents in 2015 increasing to 15% in 2016. Less than half of respondents reported the team had discussed their feelings and emotions (49% 2015, 45% 2016). Half of respondents had help with equipment at home. 11% reported no help (but needed) in 2015 compared to 7% in 2016.

All respondents appreciated the support of their OI team, reporting greater understanding of their condition and its impact on their life, reassurance of regular checks from expert professionals and having a reliable point of contact.

Conclusion:
Patient Reported Experience and Outcome Measures are a valuable tool in monitoring specialist services, highlighting areas for service development from the patient perspective.

P50
Impact of fractures on the quality of life of people with osteogenesis imperfecta
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Objectives:
Several new drugs are being tested for fracture efficacy in adults with osteogenesis imperfecta (OI). Studies have included a variety of fracture sites as outcomes. One approach is to prioritize fracture sites that are associated with worsening quality of life. We aimed to describe the association between fractures and quality of life in adults with OI.
Methods:
Data were obtained from the RUDY Study (www.rudystudy.org). This online platform captures quality of life and other outcomes, including fractures, from people with OI in the UK. The change in the EQ5D-5L summary score was calculated between the baseline and 6-month questionnaires. The group was divided into those who reported a fracture between baseline and the first 6-month follow-up (fracture group), and those who did not (control group).

Results:
28 patients (mean age 46 years, 75% female, 54% type 1 OI) completed the baseline and follow-up EQ5D-5L questionnaire (mean of 7 months later). Seven people reported a fracture in the 6-month period.

The mean EQ5D-5L score for the control group increased by +0.017. For the fracture group, the decrease in quality of life was bimodal. Four had a small positive change (mean of +0.028); they reported fractures of their lower back, toe, foot and rib. The other three had a clinically meaningful reduction of -0.182; they reported fractures of their vertebrae, ulna/radius, and hip. For the latter fracture group, the dimensions reporting the largest negative impact were pain/discomfort and anxiety/depression.

Conclusion:
In this preliminary analysis, having a fracture as an adult reduced quality of life as measured by the EQ5D-5L. This reduction was present only in those with fractures at major sites.

Take home message:
Clinical trials in OI should be powered to detect changes in fractures at major skeletal sites, although further work is needed to confirm these findings.

P51
Osteogenesis Imperfecta: The role for psychology in newly diagnosed infants and their families
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Background
For newly diagnosed infants with Osteogenesis Imperfecta (OI) classified as ‘Severe, Complex and/or Atypical’ (SCA), early initial assessment from Clinical Psychology is now being trialed by psychologists within the National SCAOI service in the Sheffield Children’s Hospital and Great Ormond Street Hospital. This assessment aims to provide families of newly diagnosed infants information, support and intervention to enhance bonding/attunement, adjustment to diagnosis and parenting skills, with a view to supporting healthy development of the infant and wider family system over the longer term.

This case series of psychological assessments will be used to illustrate the benefits of psychology input with young infants.

Method
Clinical management involved initial psychosocial assessment, formulation and follow-up interventions. All cases were referred to psychology following diagnosis by the medical team in line with protocols developed by the Highly Specialist OI National Service. The infants were aged 6 weeks - 11 months with diagnoses of OI.

The psychology assessment comprised an appointment with parent(s) and infant involving a full history of diagnosis, emotional adjustment, background and social circumstances, development, coping strategies and hopes for the future.

Results
Shared formulation with families enabled difficulties to be contextualised and understood as part of a normal process of adjustment.

Assessment of social circumstances and mental health enabled appropriate and timely onward referral into adult mental health to ensure optimal outcome for parents and infants.

Hopes and expectations were considered carefully and interventions such as sleep and play plans were developed and adapted to individual needs.

Discussion
Psychological assessment is a valuable and sensitive part of the initial intervention with infants diagnosed with OI within Highly Specialist SCAOI...
Services. Reflections on the process of developing this assessment and intervention protocol will be shared.

Take Home message
Psychological assessment/intervention in newly diagnosed infants and their families improves outcomes.

P52
‘Play with me please’
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Objectives
To present a case example of a ‘play plan’ developed from a multidisciplinary team (MDT) intervention for an infant seen within the Sheffield Children’s Hospital (SCH) as part of the National Service for Severe, Complex and Atypical Osteogenesis Imperfecta (SCAOI).

Method
Assessment: Following early MDT assessment further assessment was conducted during a visit to SCH when the infant continued to be an in-patient in their local PICU at 10 months of age and concerns were raised by parents and physiotherapy regarding appropriate stimulation.

Intervention:
A ‘Play Plan’ was developed and shared with the local PICU. An MDT approach in creating the plan was taken with Occupational Therapy & Physiotherapy input as well as discussion with the whole MDT. The play plan consisted of a schedule with activities such as bubble time, singing and story time daily, similar to that of a daycare nursery.

Results
Evaluation: The Play Plan was found to be helpful by staff in the PICU and family and a schedule revision was conducted at 18 months of age following a play assessment and Bayley’s assessment. This enabled new developmental challenges to be incorporated which promoted gross and fine motor skills as well as cognitive development such as the inclusion of ‘treasure basket time’.

Family Feedback: Parents reported feeling supported and enabled by the MDT support and play plans which helped them connect with local services in a positive approach. It also greatly supported parents connecting with their baby and brought a sense of normality to very difficult circumstances.

Summary
‘Play Plans’ may be useful and important in supporting optimal development for infants staying in hospital for long periods.

Take Home Message
‘Playing isn’t just for fun!’

P53
Stakeholder attitudes towards prenatal and postnatal mesenchymal stem cell infusion for Osteogenesis Imperfecta
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Objectives
Fetal mesenchymal stem cell infusion holds great potential for the treatment of Osteogenesis Imperfecta (OI), as it is anticipated that these cells will engrave in bone and make healthy collagen. Within the Boost Brittle Bones Before Birth (BOOSTB4) clinical trial, which is investigating the safety and efficacy of using prenatal and early postnatal stem cell infusion for severe types of OI, we are exploring stakeholder views to understand perceived benefits or concerns, identify ethical issues and establish what information and supports could be needed for implementation.
Methods
Semi-structured qualitative interviews are being conducted with four participant groups; 1. Parents and carers of children affected with OI; 2. Young people and adults affected with OI; 3. Health professionals; 4. Patient advocates. Interviews are being digitally recorded, transcribed verbatim and analysed using thematic analysis.

Results
Interviews are ongoing with 24 conducted to date. Views towards stem cell infusion for OI are generally positive. Early treatment was thought to be advantageous for reducing severity by avoiding fractures at a time of rapid bone development and could bring psychological benefits for parents, as it offers hope. Common concerns were procedure safety, short/long-term side effects, and whether infusions would work as expected. Difficulties inherent in decision-making about stem cell infusion were frequently discussed, as treatment efficacy is currently unknown and, by necessity, parents will be making decisions at a time when they are more vulnerable and potentially willing to “do anything” to help their child. Participants felt counselling and support needs may differ where there is a family history of OI or a new and unexpected OI diagnosis.

Conclusions
Good communication, significant support and time for reflection during the decision-making process will be crucial to allow parents to make informed decisions about prenatal or early postnatal stem cell infusions in the management of OI.

P54
Paediatric Osteogenesis Imperfecta
National Team (POINT); a United Kingdom multidisciplinary working group
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POINT Therapy, Nursing, Psychology and Social work Teams 1,2,3,4,5. 1Great Ormond Street Hospital for Children; 2Birmingham Children's Hospital, 3 Bristol Royal Hospital for Children; 4 Sheffield Children's Hospital 5 Brittle Bone Society, UK.

Objective
POINT is a collaborative working group comprised of physiotherapists, occupational therapists, nurses, psychologists and social workers, who work towards improving the management and care of children with Osteogenesis Imperfecta (OI).

Method
Membership of the group comprises of four highly specialised paediatric services for children with OI and from other United Kingdom (UK) centres involved in their care. There is representation from the Brittle Bone Society, (BBS), the national family support group and the work of the group is sanctioned by their Medical Advisory Board.

The group has grown from a membership of 5 in 2000 to over 30 in the present day and meetings are held 6 monthly at various venues across the UK. Meetings have a structures programme with a rotational chair and secretary.

Results
The content of the meetings include; networking within professional groups to provide peer support, developing information leaflets, discussing outcome measures, research and case studies. This has provided clinicians within a rare disease group to form collaborative working relationships across UK.

The group supports the BBS at events and with activities for people with OI throughout the year.

The group is instrumental in promoting and maintaining standards required by the highly specialised National Health Service (NHS), commissioned for Children with OI.

Conclusion & take home message
The collaborative working of the POINT group contributes towards the provision of high quality information, resources and advice relating to the management of children with OI that is accessible, to families and professionals throughout the UK.
P55
The National Hospital Discharge Survey Does Not Provide Reliable Estimates of Spinal Fusion Rates for Patients with Osteogenesis Imperfecta
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Objective:
The aim of this study is to investigate changes in the surgical frequencies performed in patients with Osteogenesis Imperfecta (OI) for intervertebral disc disorders (IVDD) and spinal stenosis SS between 1994 and 2007 in the United States using the National Hospital Discharge Survey (NHDS).

Summary of Background Data:
Epidemiologic studies evaluating national practice patterns for OI patients is limited. Evaluating prior trends in spine surgery may improve health care delivery for this group of patients.

Methods:
The National Hospital Discharge Survey was queried to identify all patients admitted to US hospitals with an OI diagnosis code (756.61) in any diagnosis column. The data file was further refined to include only cases with a diagnosis of either IVDD or SS. Remaining cases were coded to identify whether patients had undergone a laminectomy, discectomy, or spinal fusion procedure.

Results:
Of the 334 cases presenting an OI diagnosis, only 7 satisfied remaining inclusion criteria. Further analysis of trends, comorbidities, and in-patient complications was not possible due to the number of included cases falling short of the NHDS minimum necessary (30) for generating reliable nationwide estimates.

Conclusions:
While countless other conditions and procedures are able to track trends and rates, our study highlighted a reporting discrepancy in the NHDS for OI patients between 1990 and 2007. It is unclear if this is due to the nature of the randomization of the NHDS composition, or due to inconsistent medial coding. These findings aids hospital administration, policy-makers and OI caregivers in allocating health care resources to ensure the tracking and delivery of quality patient care.

P56
Spirometric assessment of pulmonary function in OI - results from a multicenter study from the Linked Clinical Research Centers and the Brittle Bone Disorders Consortium
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Pulmonary involvement is a major contributor to the morbidity in moderate-to-severe forms of osteogenesis imperfecta (OI). However, to date, only few studies have systematically investigated the pulmonary function in OI. We analyzed spirometric data from a large cohort of individuals with OI enrolled in a natural history study conducted by The Linked Clinical Research Centers (LCRC), a network of five clinical centers across North America. Spirometry data were available on 217 individuals (OI types I n=107; type III n=38; type IV n=55; and other OI subtypes n=17). Forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) were collected in systematic manner across all clinical sites. Raw values for FVC, FEV1 and FEV1/FVC were measured and the predicted values were calculated using method described by Hankinson and colleagues. Individuals with OI type III had lower raw FEV1 and FVC compared to OI types I and IV. In pooled data from the cohort, in OI types I and IV, the raw and predicted values for FVC and FEV1 followed a pattern that was consistent with the normative data from the general population. However, individuals with OI type III demonstrated consistently low volumes that did not follow the normal population pattern. In spite of the low lung volumes, the normalization of the raw values to generate percent
predicted values revealed that the volumes are “appropriate for the stature”. These results show that raw volumes measured longitudinally may be a better marker of pulmonary capacity in OI as compared to percent predicted values. Through the Brittle Bone Disorders Consortium, we are collecting longitudinal data that could help better understand the pulmonary functions in OI.

P57  
Osteogenesis Imperfecta and breastfeeding  
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Objectives
Nowadays, breastfeeding is usually not recommended in women with OI because of uncertainty about the effect on bone density and fracture rate of mothers with OI. This retrospective cohort study aimed to arrive at a more evidence based advice regarding breastfeeding.

Methods
65 women with OI (OI type 1 (n=54), OI type 3 (n=1) and OI type 4 (n=10) were included in the study. Outcome measures were: mean amount of fractures per year, amount of fractures first year postpartum and back symptoms.

Results
Fractures
Mean amount of fractures a year appeared to be lower after pregnancy than before (0.22 vs 0.55, p<0.01). There was no significant difference between the group of women that had breastfed. In the group of women that had breastfed, the risk to have a fracture in the first year postpartum was not significantly increased.

Back complaints
An increase of back complaints was noted after pregnancy (p<0.01). Women that had breastfed were noted to have a non-significant increase of back complaints.

Conclusion
No significant effects of breastfeeding on the outcome measures mean amount of fractures per year, amount of fractures first year postpartum and back symptoms. Although this study has limitations e.g. the absence in many patients of DEXA measurements before and after pregnancy, it does not generate data that support the negative advice regarding breastfeeding in women with OI. However, before a definite evidence-based advice can be given, the results of larger studies will have to be awaited.

Take home message:
Our retrospective cohort study did not generate data that support the negative advice regarding breastfeeding in women with OI.

P58  
Improvement of dietary calcium intake in Osteogenesis Imperfecta children after nutritional intervention  
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OBJECTIVE:
To perform nutritional intervention (NI) and evaluate dietary calcium intake in pediatric patients with Osteogenesis Imperfecta (OI).

METHODS:
Both genders, aged between 2 and 18 years old were enrolled. NI was carried out through a nutritional consultation followed by a personal nutritional orientation, including recipes rich in calcium. Calcium intake was assessed before and after NI using a food frequency questionnaire (FFQ) adapted to calcium intake for foods high in calcium content such as milk, yogurt and cheese. Values
obtained from the FFQ were compared with Estimated Average Requirement (EAD) and Recommended Dietary Allowances (RDA) for age to establish the percentage of adequacy of intake. FFQ were composed by: milk (1 cup= 175ml), 1 yoghurt (120ml), ricotta or white cheese (1 medium slice=30g), mozzarella cheese (1 slice=22.5g) and classified according to the consumption: daily, weekly or monthly, number of times of 1-10/day and size of the portion according to a illustrative.

RESULTS:
52 patients were evaluated, 29 were female and mean age was 50.83 ± 129.48 months. Calcium intake at baseline were 706 ± 325mg and after NI were 885 ± 265mg (p <0.001). Regarding calcium intake adequacy there was significant difference (p <0.001) from baseline to after NI for both parameters EAD (66% to 81%) and for RDA (from 56% to 69%). CONCLUSION: Calcium plays an important role in the development and maintenance of bone health. Studies have been shown low calcium intake in OI subjects, compromising bone mineral density and increasing risk factors. In this study, it was observed an increased calcium intake, after nutritional intervention, showing the importance of nutrition in the multidisciplinary treatment of OI.

Take home message:
Calcium plays an important role in bone health and calcium intake can be encouraged in children with OI using simple method.

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P59
Comparison between temporal bone CT and hearing in OI
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Objectives
This study attempts to determine whether temporal bone computerized tomodensitometry (CT) reveals asymptomatic ear damage in Osteogenesis Imperfecta (OI), to assess how temporal bone CT-scan aspects are related to hearing loss type and degree in OI, and to investigate the predictive value of CT over an 8 year audiometric follow-up.

Material and methods
44 patients affected by OI underwent audiometry, acoustic reflex measurements, and temporal bone CT. Stapes footplate and perilabyrinthic CT aspects were scaled by two examiners. Correlation between hearing and CT-scan parameters was investigated.

Results
In a significant proportion of ears CT results were conflicting with hearing data: hearing was subnormal 10 ears with a thickened footplate and 6 ears with significant peri-cochlear demineralization; conversely no CT anomaly was found in 15 ears with conductive hearing loss (HL) and 20 ears with sensorineural HL. Incus and malleus hypodensities were observed in several cases with post-operative conductive HL. A significant difference in hearing thresholds was established between groups of ears with various CT lesion degrees. A quicker progression of hearing over an 8-year time was also shown in ears with CT anomalies than in ears with normal CT.

Conclusion
It cannot be predicted from audiogram and tympanometry which CT aspect will be found. But CT anomaly might be an early sign of future hearing deterioration.

P60
OSTEOGENESIS IMPERFECTA: DIFFICULTIES FOR A CORRECT FOLLOW-UP AND ASSESSMENT OF RESPONSE TO TREATMENT
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INTRODUCTION:
Osteogenesis imperfecta (OI), is a hereditary rare

disease characterized by the presence of changes in

the amount, structure or Type 1 collagen

processing. It shows a great heterogeneity from the

clinical perspective, with very severe cases with

very premature osteoporosis, bone fractures, which

is going to produce frequent surgeries and

secondary deformations. In addition, these patients

are usually short and have serious cifoscoliosis.

During the initial evaluation and monitoring, the

most useful test to evaluate the bone condition is

the bone mineral density (BMD) measured by DXA.

However, this test is invalid and no valuable in

many cases due to the presence of osteosynthesis

material in spine, femur or both from previous

surgeries or deformities, making the valuation of

treatment’s responses difficult.

MATERIAL AND METHODS:
We choose some cases with severe forms of OI with

no valuable densitometria due to deformities or

osteosynthesis material. Photos were taken.

RESULTS:
Cases with important deformations are included

below (Figures), along with very variable BMD

results not corresponding to real changes in BMD

but the difficulties to measure it.

CONCLUSIONS
The OI is a rare disease with a great clinical

heterogeneity, although the presence of bone

fragility with osteoporosis, multiple fractures and

deformities are quite common. This involves in the

difficulty to measure the BMD by means of DXA in

most of the cases, which makes a correct initial

evaluation and a treatment’s response even more
difficult.

It’s necessary provide new methods allowing BMD

evaluation of these patients.

P61
Brazilian Network of Osteogenesis Imperfecta

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Brazil

Introduction:
In Brazil, there is no official epidemiological data

regarding OI or other outcomes. In 2001, 10

Reference Centers for Treatment of OI (CROI) were

established by Ministry of Health of Brazil aiming to

implement and regulate guidelines for treatment of

OI. Although there are currently 11 CROIs registered

in Brazil, since their creation, these have been

working isolated.

Objectives:
This project aims to: 1) structure an organized

national network of reference and counter-

reference for research, diagnosis and management

of OI in Brazil; 2) establish a Brazilian Registry of OI;

3) to create a molecular analysis center.

Methods:
In this prospective cohort study, all CROIs were

invited to participate and individuals of any age and

gender with clinical diagnosis of OI are included.

This multicenter project was approved by the

Research Ethics Committee at the Coordinating

Center (Hospital de Clínicas de Porto Alegre/ CAAE

47277215.8.1001.5327), and all patients or

guardians signed an informed consent form.
Results (initial):
So far, 6 CROIs, from 5 different states are participating of the study and also have the approval of their local Ethics Committee. Each CROI has its own coordinator and multidisciplinary team and have been active for the past 8-15 years. Three of these CROIs assist children and adults, 2 CROIs only children and 1 only adults. The number of OI cases registered at each of the CROIs varies between 45 and 208, totaling more than 700 patients with OI.

Conclusion:
Therefore, the development of a national registry will lead to the creation of technical-scientific foundations for public health policies and in the future will allow a joint international analysis of the similarities and differences between populations.

Take home message:
Efforts to evaluate the natural history, morbidity, mortality and effectiveness of treatment are fundamental in OI and prospective follow-up studies are urgently necessary.

P62
EXPERIENCE OF THE GETAFE UNIVERSITY HOSPITAL IN THE TREATMENT OF IMPERFECT OSTEOGENESIS
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OBJECTIVES
Analyze the experience of our hospital in the medical and surgical treatment. Review of the number of patients and their clinical situation.

METHODS
We have reviewed computerized surgical records, hospital admission data, and outpatient visits. We include patients from the departments of adult endocrinology, pediatrics and orthopedic surgery and traumatology (OST).

RESULTS
At present, medical services have 92 children and 51 adults in monitored and the OST department has 160 patients.

The treatment with zolendronate has been substituted for pamidronate and currently there are only 4 patients with pamidronate. Three patients have denosumab.

Among adults, the treatment applied is more varied.

A bone densitometry, abdominal ultrasound, and bone age, are performed one time a year. All patients are submitted to an echocardiogram and an ophthalmology study.

Also, we do eudiometry studies from 7 years old and spirometries in patients with a thoracic or spinal deformity.

We have performed 260 surgeries in more 400 processes in long bones. 85% were children. 279 long bones of MMII, 25 Hips with the Wagner-Finidori method and 220 telescopic nails. We has had only two bone infections.

All our patients have overcome at least one step more of independency.

CONCLUSIONS
Not all patients whit OI need treatment.

Medical treatment reduces pain and improves quality of life.

The best results are obtained when the treatment is initiated at an earlier age: the treatment changes the natural course of the disease.
Surgical treatment is indicated for the correction of deformities and it is performed more frequently in the treatment of fractures because it reduces the time of immobilization and it allows walking before.

P63
Development of an osteogenesis imperfecta-specific quality of life measure
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Objectives:
Osteogenesis imperfecta (OI) is an hereditary disorder affecting approximately 1 in 20,000 births. There is currently no disease-specific quality of life (QoL) measure for children with OI. This study used a mixed methods approach to develop a QoL measure for the paediatric OI population. Patient reported outcome measure development is an iterative process, moving back and forth between concept elicitation, questionnaire development, pre-testing and psychometric analysis.

Methods:
In order to encourage a balance between good content validity, alongside promoting a robust, reliable and responsive measure, the methods chosen involved:
- Literature review to ensure no suitable QoL measure already existed and to begin eliciting themes.
- Interview and focus groups with the target population to uncover relevant concepts and develop a conceptual framework.
- Questionnaire development; transforming themes into items, using the children’s’ language ensuring high content validity and acceptability.
- Pre-testing the instrument alongside a sample of the OI population, making revisions as required.
- Psychometric evaluation to assess validity, reliability and responsiveness of the questionnaire, informing potential item elimination and questionnaire revision.

Results:
Interviews and focus groups with the target population uncovered six main themes when describing QoL in children with OI; being safe and careful, reduced function, pain, fear, independence and isolation. These themes informed the development of the conceptual framework, which alongside the children’s own thematic based quotes, was used to develop the OIQoL. Pre-testing of the OIQoL highlighted logistical issues and understanding, which lead to revisions of the initial version.

Conclusion:
Cronbach’s alpha for the 39-item questionnaire was 0.86. Concerns surrounding construct validity and internal consistency reliability highlighted the need to re-word some items and eliminate others, resulting in a 33-item questionnaire.

Take home message:
The 33-item OIQoL questionnaire is available for use in children with OI.

P64
Autism in Osteogenesis Imperfecta: a true association?
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Objectives
Osteogenesis Imperfecta (OI) is a heterogeneous condition mainly characterised by bone fragility; intelligence is reported to be normal. However, a minority of children seen within Sheffield National OI Service also show symptomatology consistent with an ‘Autism Spectrum Disorder’. A joint Genetics and Psychology research study was undertaken to identify these patients using ‘Gold Standard’ research tools (Autism Diagnostic Inventory Revised (ADI-R); Autism Diagnostic Observation Schedule (ADOS)) and undertake genetic analyses in them.
Method
A cohort of children with autistic traits and severe/complex OI where recruited to the study.

ADI & ADOS
Standardised tools were used to confirm autism diagnosis. ADI and ADOS were completed by the Clinical Psychologist; ADI comprises a 93 item semi-structured clinical review with a diagnostic algorithm diagnosing Autism; ADOS is a semi-structured assessment of socialisation, communication and play/imagination for assessing autism.

Exome Sequencing
In patients recruited, those that fulfilled research criteria for diagnosis of autism using above tools (n=5) were recruited to trio whole exome sequencing (WES).

Results
WES studies are ongoing; so far Patient 1 has compound heterozygous variants in NBAS; Patient 2 has variant in NRX1; Patient 3 has a PLS3 variant; further analysis is ongoing.

Conclusions
Identifying autism in OI had important clinical and social benefits for patients and their families in ensuring access to services, appropriate schooling, increased understanding of behaviour and support.

Take Home Message
It is important for clinicians looking after children with OI to be aware of early features of developmental delay/autistic traits especially with severe forms of OI as the emphasis is on their mobility and bone health. Ensuring appropriate assessment and access to services early-on will enable these patients achieve their potential. Further investigations of genomics in OI in relation to autism are required and dual diagnosis is essential for high quality clinical and educational provision.

P65
Central Venous Access Device (CVAD) complications in children with Osteogenesis Imperfecta (OI).
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POINT Therapy, Nursing, Psychology and Social work Teams 1,2,3,4,5. 1Great Ormond Street Hospital for Children; 2Birmingham Children's Hospital, 3 Bristol Royal Hospital for Children; 4 Sheffield Children's Hospital 5 Brittle Bone Society, UK. Objective POINT is a collaborative working group comprised of physiotherapists, occupational therapists, nurses, psychologists and social workers, who work towards improving the management and care of children with Osteogenesis Imperfecta (OI).

Method Membership of the group comprises of four highly specialised paediatric services for children with OI and from other United Kingdom (UK) centres involved in their care. There is representation from the Brittle Bone Society, (BBS), the national family support group and the work of the group is sanctioned by their Medical Advisory Board. The group has grown from a membership of 5 in 2000 to over 30 in the present day and meetings are held 6 monthly at various venues across in the UK. Meetings have a structures programme with a rotational chair and secretary.

Results The content of the meetings include; networking within professional groups to provide peer support, developing information leaflets, discussing outcome measures, research and case studies. This has provided clinicians within a rare disease group to form collaborative working relationships across UK. The group supports the BBS at events and with activities for people with OI throughout the year. The group is instrumental in promoting and maintaining standards required by the highly specialised National Health Service (NHS), commissioned for Children with OI. Conclusion & take home message The collaborative working of the POINT group contributes towards the provision of high quality information, resources and advice relating to the management of children with OI that is accessible, to families and professionals throughout the UK.
P66
Genetic screening of 180 Osteogenesis Imperfecta patients with NGS technologies

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Objectives
The coming out of Next Generation Sequencing (NGS) technologies, with documented advantages and reduced costs respect to Sanger sequencing, has provided new appealing approaches to diagnostic testing. Its use for routine diagnostic purposes requires certification in terms of reliability. To test the feasibility of using the Ion Torrent Personal Genome Machine (PGM, Thermofisher) in clinical diagnosis, we assessed its performance to detect point mutations and large rearrangements, for evaluating the concordance with our traditional genetic screening.

Methods
180 patients affected by Osteogenesis Imperfecta (OI) have been enrolled in this project and analyzed through targeted sequencing, performed with Ion PGM System (Thermo Fisher Scientific). 2 custom panels were created through the Ion AmpliSeq™ Custom Designer. 150 individuals have been tested for the presence of point mutations and complex rearrangements in COL1A1/A2 and IFITM5 genes (OI panel_1); 30 patients have been screened for CRTAP, LEPRE1, PPIB, SERPINF1, SERPINH1, FKBP10, SP7, WNT1, PLS3, PLOD2, BMP1, CREB3L1, LRPS and TMEM38B genes (OI panel_2). All of them have been previously analyzed with standard techniques (dHPLC, Sanger sequencing and MLPA).

Results
Except than for those regions not covered by the designed OI-panel – which will continue to be analyzed by Sanger sequencing – the NGS molecular screening showed a good accordance to the standard techniques in the point mutation detection. It was identified 41 pathogenic variant in COL1A1 gene, 43 in COL1A2, 2 in IFITM5, 3 in LEPRE1, 3 in CRTAP, 2 in SERPINF1, 1 in FKBP10 and 1 in WNT1. Multi-exon deletion analysis is ongoing.

Conclusion and take home message
As expected, the potential of the new NGS technologies has been verified. Besides validating a good accordance between NGS and standard techniques in detecting OI-related mutations, its use guarantee also a cost reduction and a referral time decrease, so becoming a good option for genetic diagnosis.

P67
The Registry of Osteogenesis Imperfecta (ROI): open the Italian experience to international scenario

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The idea of a Registry of Osteogenesis Imperfecta (ROI), formally established in 2013, arose from the need to overcome the difficulties of clinical and genetic data storage and analysis. The common way to collect patient information is frequently chaotic, inconvenient and sometimes unsafe, particularly in rare diseases (RDS) scenario.

In March 2003, the Medical Genetics Department activated a Day Clinic starting the collection of data from patients/families affected by RDs. In following years, we directed our efforts to optimize data and, in 2008 with a software-house, we designed and realized a patient registry platform to improve management of persons affected by OI and other RDs and to help researchers in analysing information. This platform, “GePhCARD” (Genotype-Phenotype Correlation, Analyses & Research Database) is a multi-client system, allowing secure data storage, retrieval and rationalization. It is articulated in sections, strongly related and mutually dependent on each other, corresponding to personal, clinical, genetic and genealogical domains. This approach corroborates and integrates data from different resources and diseases aspects, helping in correlating genetic and
phenotypic characteristics. To date, information of 700 patients has been collected (> 100 enrollments during 2016) and with the support of ASITOI Onlus, we are working to create an Italian consortium, sharing instruments like ROI.

Nowadays, with the support of the Directive 2011/24/EU and the active European efforts in stimulating the creation of European Reference Networks (ERNs) for RDs, there’s a need of pooling information of larger datasets. As ERN BOND coordinator, we are stimulating improvement processes for patients’ diagnosis, treatment and care; one step already in place is the participation to “Rare diseases - support for New Registries” Call, 3rd Health Programme with “FREBO” (Federated Registry of Bone Fragility) proposal that aims to design a data federation model on OI, starting from three European registries, including ROI. More data, better knowledge!

P68
Web-based surveys using PROMIS® instruments capture important components of the disease experience in OI
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Objectives:
All current outcome measures in Osteogenesis Imperfecta (OI) have been developed by medical experts, without input from patients. Yet, patients and clinicians often disagree on level of disease burden. As new medical, genetic, and surgical treatments become available, it is imperative to develop clinical scoring instruments which capture the disease characteristics of importance to individuals with OI in order to compare/contrast the impact of new treatments, determine future needs, and suggest topics for research.

Methods:
300 individuals with self-reported OI, representing a wide range of self-reported disease severity, were recruited from the Rare Diseases Clinical Research Network Brittle Bone Disorders Consortium (RDCRNBBBD) Contact Registry to respond to a survey utilizing Patient-Reported Outcomes Measurement Information System (PROMIS®) instruments focused on a wide range of health issues, including pain interference, mobility, and fatigue. Parent proxy surveys were provided for children.

Results:
290 individuals completed the survey, including 92 children represented by parent proxy. 94% self-identified as white. <30% had a confirmed diagnosis/type by skin biopsy or DNA. ~50% reported having affected family members. 56% walked unaided. 23% used a wheelchair. 26% reported difficulty with breathing. 38% percent reported hearing loss. 52% reported undergoing rodding surgery. 13% have required spine surgery. 53% of women over 18 had been pregnant. PROMIS® score variations suggest that the instruments can appropriately pick up most changes in QOL measures.

Conclusion:
Adults with OI vary from the general population in QOL measures. Our survey experience supports an internet-based strategy for successful patient-centered outcomes research in rare disease populations. Future research will focus on expanding PROMIS® instruments to capture the full range of the OI experience.

Take home message:
Web-based surveys using validated PROMIS® questionnaires offer the opportunity to capture the perspective of the OI community in defining the impact of treatments, unmet clinical needs, and innovative research.
Objective:
To report on dental characteristics and treatment load in Danish adult patients with osteogenesis imperfecta (OI).

Material and methods:
Oral examination of 73 genetically-verified OI patients was performed. OI types I, III and IV were represented by 75.3%, 8.2%, and 16.4%, respectively. Patients were diagnosed as having dentinogenesis imperfecta (DI) if they had clinical and radiological signs of DI. In the data analysis, mild OI (type I) was compared to moderate-severe OI (type III and IV).

Results:
Discoloration of teeth was found in patients with mild and moderate-severe OI (5.5% vs. 83.3 %, (p<0.001)). Cervical constriction and pulpal obliteration were frequent findings in patients with moderate-severe OI (61.1% and 88.9%, respectively), whereas pulp stones and taurodontism were diagnosed in mild OI patients only (29.1 % and 9.1%, respectively). Among OI patients with DI (24.7%), a considerably higher prevalence was found in moderate-severe (94.4%) compared to mild OI (1.8%) patients (p<0.001). The mean number of teeth with artificial crowns was significantly higher in patients with moderate-severe OI than in mild OI (mean: 6.1, SD 7.2, and mean: 1.4, SD 2.8, respectively) (p<0.001). The mean number of teeth with fillings in patients with mild OI was significantly higher than in moderate-severe OI patients (mean: 9.7, SD 5.1, and mean: 5, SD 4.4, respectively) (p<0.001).

Conclusions:
One fourth of OI patients had DI, and the vast majority of them had moderate-severe OI. Whereas discoloration of teeth, cervical constriction and pulp obliteration were frequently findings in patients with moderate-severe OI, pulp stones and taurodontism were found in patients with mild OI only. In patients with moderate-severe OI, the dental treatment load was dominated by prosthetic treatment, whereas restorative treatment with fillings was more prevalent in patients with mild OI.

Objective:
The purpose of this study was to assess the size of teeth in individuals with OI.

Methods.
We compared the tooth crown size between 20 OI patients (6 males, 14 females, aged 9.8 to 60.8 years) and their healthy age- and gender-matched controls. The severity of OI, presence of DI, and hypodontia were also recorded. The size of both upper and lower permanent teeth was measured from plaster models. Two-tailed t-test was used for statistical analysis.
Results.
In three of the 20 patients (15%), as compared to the controls, the teeth were statistically significantly smaller (p < 0.05). These patients had OI type I, III and IV. All of them also exhibited DI.

Conclusion.
OI patients may have significantly smaller-sized teeth, as compared to unaffected peers. A smaller tooth size can be favourable form an orthodontic point of view, since OI patients often have small dental arches in the upper jaw, which contributes to dental crowding and problems with eruption. On the other hand, small tooth size can further predispose to fracturing of teeth, which is a considerable risk faced by individuals with OI and dentin abnormality.

Take home message. A smaller than normal size of tooth crowns can apparently be listed to the dental features of OI.

**P71**
**Evaluation of Intensive Therapy for children with OI at Birmingham Children’s Hospital (BCH) – a pilot project.**
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Objectives
In 2014 we initiated Intensive Therapy (IT) for children with Osteogenesis Imperfecta (OI). Our aim is to explore it’s effectiveness, measures used and experiences of families to inform future practice.

Method
IT is an opportunity for patient and parents to attend sessions with the multidisciplinary team (MDT) over 3 days. This includes time with physiotherapy (PT), occupational therapy (OT), psychology, specialist nurses, consultant and social worker.

7 of 8 patients were initially seen in outreach clinics where time is limited for therapy. Initial assessment takes place on the first morning led by OT or PT, where expectations and goals are set which guide therapy input. Patients are seen by the MDT for treatment and education.

Patient notes were reviewed retrospectively. The assessments and outcome measures were identified together with the themes generated from feedback questionnaires which were given to patients on completion of IT.

Results
8 children (age 3-15 years) were seen over a period of 3 years; 2 patients attending twice.

7/8 patients had moderate to severe OI. Average time spent with family by the MDT was 850 minutes of which OT (mean 303) and PT (mean 287) were highest. The 6 minute walk test was the most consistent assessment tool used and Goal Attainment Scaling (GAS) for outcome measure. 5 questionnaires were completed by families post IT. Positive feedback was received from all families reporting they felt prepared, their views considered, with home goals to work on and they would recommend IT.

Conclusions
Offering IT gives a positive experience to families although formal feedback is limited. GAS goals are an appropriate method to record outcomes which are both relevant to the patient and can be used by the MDT. Greater consistency and range of functional assessments are needed to demonstrate changes in performance.

**P72**
**Evaluation of a six week therapy lead group for babies and toddlers**
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Objectives
To evaluate the benefits of a six week baby and toddler therapy led group for children with Osteogenesis Imperfecta (OI) who had been
referred to a specialised service and identified as having some developmental delay.

Methods
Ten children under the age of 2 years old were invited along with their parents to attend a therapy led group for six sessions run fortnightly. Using the Bayley scale of infant and toddler development Ill children had been identified as having some area of developmental delay.

Three individualised goals for each participant were identified prior to the intervention. Outcomes were recorded using the Goal Attainment Scaling (GAS) light model, a 6 point scale measuring the extent to which the goals were achieved following intervention.

Each session the focus was to facilitate motor and cognitive development, provide education to parents and facilitate peer interaction. Following the intervention, the goals were scored for each child and each parent was asked to complete a feedback questionnaire anonymously to gather information on what they found beneficial and ideas for future groups.

Results
Baseline and post intervention results were available for six children. All children made overall improvement, with a one point increase in at least one GAS goal. Two children did not achieve one of their GAS goals. Two children made a two point increase in one of their goals.

Feedback questionnaires were received from eight parents. These reported that the group was very beneficial in terms of building confidence, meeting other parents and contact with specialist therapists. They all said that they would like to attend for a subsequent block.

Conclusion and take home message
A six week therapy led group for babies and toddlers with OI showed measurable improvements for participants, was well received by parents and was an effective use of therapy time.

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P73
Sensory Integration Dysfunction in Osteogenesis Imperfecta: A Case Study

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Sensory Integration (SI) is a neurological process involving the reception, registration, modulation, organisation and interpretation of sensory information. Trauma and limited opportunities in early life are hypothesised to impact on SI, leading to deficits in functional behaviours.

Objectives:
To explore if SI is a useful approach in assessment and intervention for children diagnosed with Osteogenesis Imperfecta.

Methods:
Child X, a 9 year old boy, diagnosed with Osteogenesis Imperfecta was invited for assessment. He presented to the Bristol OI team at age 5 with a history of tibia, elbow and ankle fractures. Compression fractures of T1 and T5-T8 were evident. Dxa scan showed a lumbar bone mineral density score of -3.3. Clinical examination revealed blue sclera and marked ligament laxity. Subsequently, Child X received a 4 year course of bisphosphonate infusions. Bone mineral density is now within the typical range. He has had no further fractures. Hypermobility remains a prominent feature. He stands with a hyper-lordotic posture and pes planovalgus foot position. He wears dynamic ankle foot orthosis (DAFO) to provide additional support and stability to his foot position. Functional difficulties included reduced balance and motor co-ordination, poor handwriting, poor personal organisation and social immaturity. These may also be indicative of sensory integration dysfunction.

The Sensory Processing Measure (SPM) and Sensory Integration and Praxis Test (SIPT) were used to measure sensory responsiveness, praxis and discriminatory functions.
Results:
No difficulties with sensory modulation were identified on SPM. Results from the SIPT showed a pattern of dysfunction consistent with somatodyspraxia, attributable to difficulties in the proprioceptive and vestibular systems. This pattern of dysfunction impedes development of independence in daily routines and is strongly associated with poor social skills.

Conclusion & Take home message:
Sensory Integration may be a factor contributing to the functional challenges of the OI population. Further research is required.

P74
Physical activity of children with heritable disorders of connective tissue: a comparative study
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Objectives:
To investigate the physical activity participation of children with hypermobile Ehlers-Danlos Syndrome (hEDS) and Osteogenesis Imperfecta (OI).

Methods:
Fifty-five school-aged children with Osteogenesis Imperfecta and 34 children with hypermobile Ehlers-Danlos Syndrome were recruited from a tertiary clinic in 2016 - 2017. Physical activity was assessed using the Adolescent Physical Activity Recall Questionnaire. Current presenting complaints were collected via interview.

Results:
Participants had a mean age of 12.5 years (SD 2.91 years). Forty-seven percent of children undertook the recommended 60 minutes or more of moderate to vigorous physical activity per day. There was no significant difference in the minutes per week of moderate to vigorous physical activity between children with either condition (mean difference 29 minutes, 95% CI -134 to 191 minutes). Children with OI spent a significantly greater percentage of their physical activity time undertaking non-organised activity in comparison to children with hEDS (mean difference 19.4%, 95% CI 4.1 to 34.9%). Girls with Osteogenesis Imperfecta spent significantly less minutes per week being active compared to boys (mean difference 248 minutes, 95% CI 54 to 442 minutes). There was no gender difference in participation of children with hEDS. The most common physical activities were swimming and walking in both groups (> 40% participation).

Conclusion:
Over half of children with heritable disorders of connective tissue don’t meet daily physical activity recommendations. When participating, most children undertake low impact activities and children with OI spend a greater proportion of their time in non-organised activities. Girls with OI are the least active group.

Take-home messages:
Health professionals working with children with OI should tailor interventions to increase physical activity for girls.

P75
Functional walking ability of children with Osteogenesis Imperfecta
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Objectives:
To investigate the functional walking ability of children with Osteogenesis Imperfecta (OI) in comparison to their healthy peers, and to
determine the extent to which disease characteristics affect performance.

Methods:
61 school-aged children with OI were recruited from a tertiary clinic for this cross-sectional study. Functional walking ability was assessed with the six minute walk test and the timed up and go test. Medical history was collected via interview and review of patient records including recent dual energy xray absorptiometry results. Unpaired t-tests compared results to contemporary normative data and stepwise linear regression investigated the contributions of disease characteristics to performance on each measure.

Results:
Participants included children with Type I (n=30), Type III (n=5), Type IV (n=26) and Type V (n=1) OI, with a mean age of 11.71 years (SD 3.75 years). Children with OI had reduced functional performance on both measures compared to their healthy peers: six minute walk test (mean difference -111 metres, 95% CI -150 to -72 metres), timed up and go test (mean difference -0.56 seconds, 95%CI -0.23 to -0.89 seconds). Forty-seven percent of the variance in the six minute walk test distance was explained by lean tissue mass ( = 0.6) and number of unstable joints reported by children ( = -0.26) (p < 0.001). Lean tissue mass ( = -0.41) explained 17% of the variance in the time to complete the timed up and go test (p = 0.006).

Conclusion:
Children with OI have reduced walking ability compared to healthy peers. Greater lean tissue mass is essential to maximise walking performance.

Take-home messages:
When aiming to improve walking ability, treating physiotherapists should prioritise increasing muscle mass and improving joint stability.

P76
Parents and therapists working in partnership: a questionnaire to explore parent perceptions of the impact of a Connective Tissue Dysplasia on their child's daily functioning.
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Objectives:
To investigate parent perceptions of the impact of a Connective Tissue Dysplasia (CTD) on the daily life of children as symptoms associated with a CTD can have a negative impact on a child’s daily participation.

Methods
A cross sectional survey of parents of children with Osteogenesis Imperfecta (OI) and other CTDs (Ehlers-Danlos Syndrome, Marfans Syndrome and unclassified CTD) was undertaken between February and December 2016 at a tertiary clinic at The Children's Hospital at Westmead, Australia. Questions addressing the effect of characteristics of a CTD, including joint pain and fatigue, on self-care, school and leisure participation were included.

Results
135 surveys were distributed with 78% returned (53% male, mean age 12.7 years). Parents of children with OI made up 40% of the sample, reporting pain and fatigue equally as the most prevalent characteristics (60%). Parents of children with OI reported their child is usually as independent as their peers when performing self care activities (86%) significantly more frequently than when participating in school activities (62%) (p<0.001). When participating at school, handwriting speed (21%) and engaging in gross motor activities (24%) were the most problematic tasks for children with OI. Outside of school, children with OI have significantly greater difficulty spending time with friends compared to children with other CTD’s (OI 45%, other CTD 23%, p=0.04).

Conclusions
Overall, parents reported difficulties with daily participation for their children with a CTD condition. Specifically, children with OI require strategies to reduce CTD symptoms to improve school participation and maximise time with friends outside of school. Therefore, health professionals
should work with parents to prioritise goals that will maximise daily participation for children with a CTD.

Take home message:
Health professionals need to pay more attention to parent perceptions of school and leisure activities when assessing participation of children with OI.

P77
A cross-sectional multicenter study of mobility in osteogenesis imperfecta in North America
A cross-sectional multicenter study of mobility in osteogenesis imperfecta in North America
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Objectives:
To analyze various aspects of mobility to better understand natural disease history and improve patient care.

Methods:
The LCRC is comprised five clinical sites with significant experience treating OI. Mobility data was collected in accordance with detailed instructions and included age at first walking, Gillette Functional Assessment Questionnaire (FAQ), and 6 minute walk test (6MWT), analyzed for subjects 3+ years old. Statistical analysis was performed using one way ANOVA, adjusted to control for age.

Results:
A total of 480 subjects were identified with six OI types: 217 Type I, 85 Type III, 137 Type IV, 16 Type V, 10 Type VI, 4 Type VII, 11 unclassified. The analysis revealed statistically significant differences between Types I, III, and IV for all tests (p<0.001 age @ first walk, FAQ p=0.0076 for 6MWT). Limited subject numbers prevented comparisons between the other types. Age did not impact on any factors tested. The FAQ results revealed a majority of individuals with Type I OI could perform tasks including taking a step backwards (98.1%) and walking while carrying an object (99.1%). In contrast, 36.1% and 39.8% of individuals with Type III OI could perform these tasks, respectively. Individuals with OI were most limited in the ability to jump rope (63.0% of Type I, 3.6% of Type III) and ice/roller skate (33.2% of Type I, 2.4% of Type III)

Conclusion:
The results illustrate differences in mobility for OI types. It is well-recognized that multicenter studies in rare diseases can lead to a better understanding of the natural disease history, generate further research hypotheses, and provide better therapeutic options.

«Take home message»
The prognosis of a child with a particular OI type is of clinical interest, particularly when setting rehabilitation goals. Understanding disease related characteristics specific to each class allows for more accurate patient comparisons and expectations.

P78
Assistive Seating Device for Infants with Osteogenesis Imperfecta
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Introduction
Infants with severe osteogenesis imperfecta (OI) require careful handling, which is a challenge for caretakers. These infants are often limited to lying flat on a pillow to minimize risk of vertebral
compression fractures; however, providing infants with opportunities to be upright and interact with the world is crucial for their mental and physical development. Currently, no specialized seating devices exist for infants with OI that allow them to sit up, supported at various angles.

Objective
The goal of this project was to create an adjustable seating device that will support the body of infants with OI while allowing them to engage with their surrounding environment.

Methods
The first generation prototype includes a reclining mechanism controlled by a handle on the side of the chair, a two-part aluminum frame, two plastic shells covering the aluminum frames, memory foam with cooling gel as the padding material, and a five-point restraint system. The prototype also features a 2-in-1 detachable, adjustable frame attached to the chair back for adding a tray or hanging toys.

Results
This first generation prototype is adjustable and gives the infant an opportunity to engage with the world around them. It can hold up to 50 pounds and is long enough to support the entire body of an infant with OI.

Conclusion
Design iterations for the second generation prototype are currently underway and include implementing a ratcheting mechanism and a 2-in-1 tilt-in-space design. The ratcheting mechanism will make the chair more user friendly, while the 2-in-1 tilt-in-space design will provide added functionality to be upright without flexing the spine.

Take Home Message
With these design modifications and further testing, this assistive seating device will address an unmet need identified by caretakers and will help infants with OI safely engage with their surrounding environment.

P79
Using the Bayley Scales of Infant and Toddler Development to assess a child with Osteogenesis Imperfecta.
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Objectives
Osteogenesis Imperfecta (OI) is most commonly caused by a defect in the genes which produce type 1 collagen. Features of OI include fractures, bony deformities and ligamentous laxity. It is our clinical experience that some children with OI have delayed gross motor development.

There are no established valid and reliable outcome measures to assess infant/toddler development in OI. The Bayley Scales of Infant and Toddler Development (Bayley III) is an individually administered instrument that assesses the developmental functioning of infants and young children aged 1 month to 42 months of age. The Bayley III consists of 3 administered scales: Cognitive, Language and Motor.

Therapists from a highly specialised centre for paediatric OI used the Bayley III to assess the development of a child with severe OI. This allowed investigation as to whether this assessment may be an appropriate tool to use with the OI population and whether it may identify gross motor delay.

Methods
The Bayley III was administered by an occupational therapist and physiotherapist on a child with severe OI, at ages 9 months, 18 months and 24 months.

Results
At each age interval, the child achieved a scaled score within the average range in the cognitive, language and fine motor scales. The child achieved a scaled score well below average for the gross motor scale.
Conclusion and Take Home Message
The Bayley assessment was an appropriate assessment tool to use with this child with severe OI. The child presented with gross motor delay but interestingly this has not impacted on the other tested areas of development.

More research is needed to establish developmental trends in OI. Further use of the Bayley III with children of varying severity of OI and at different age intervals, may identify some strengths and/or limitations.

P80
Severity and Impact of Fatigue in people with Osteogenesis Imperfecta
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Objectives
The objective of this study is to investigate the hypothesis that the impact of fatigue in patients with OI is greater than in the general healthy population.

Methods
Patients with a clinical diagnosis of OI and age ≥ 18 years were asked to participate. To evaluate the impact of fatigue in these patients, the Fatigue Severity Scale (FSS) was used. This is a 9-item scale which measures the severity of fatigue and its effect on a person’s activities and lifestyle. The questionnaire was created as an app and a link was sent to the participants. Medical records were analyzed from patients who filled in the FSS.

Results
A group of 151 patients consented to participate and 99 patients responded and consisted of people with OI type 1,3 and 4 (OI type 1 (n=72), OI type 3 (n=13) and OI type 4 (n=14). Furthermore, 61 women and 38 men were included. Mean age was 46 years ranging between 19-81 years. The total group of OI patients scored 4.0 on the FSS.

Interestingly, this score was not very variable between people with different OI types or between people from different age groups. We compared the results of the FSS score with results of patients with other chronic conditions and the general healthy population (mean score FSS 2.3)

Conclusion
Results from the FSS confirm the hypothesis that the severity and impact of fatigue in people with OI is greater than in the general healthy population. As fatigue is often raised by people with OI as a factor that significantly decreases their quality of life, outcome of FSS could be an important indicator that reflects quality of care for OI patients.

Take home message
Severity and impact of fatigue in people with OI is greater than in the general healthy population.

P81
The elbow in type V osteogenesis imperfecta: is early functional loss related to radiographic findings?
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Objectives:
Type V osteogenesis imperfecta (OI) results in abnormal modelling of the ulna, radial head dislocation and interosseous membrane calcification (IOM). Individuals develop reduced functional ability as a consequence of reduced range of movement (ROM) including elbow flexion and/or supination. We describe the evolution of radiographic and functional parameters in a cohort seen in our centre.

Method:
We performed a retrospective review of all our type V OI cases. ROM data included earliest loss of elbow flexion (≤120°) and supination (≤60°). Radiographic images were double reported, consensus reached in cases of discrepancy. Earliest age of onset was
determined for radiographic features: IOM; subluxation (SUBL) or complete dislocation (DISL) of radial head; abnormal modelling of proximal ulna (ULNMd); and ulna bowing ≥15° (UBOW15).

Results
13 cases were reviewed (6 male/7 female; mean age 6.5yrs (0.3-16.8yrs)).

Loss of flexion and supination occurred in 12 elbows (6/12 children) and 14 elbows (8/12 children), respectively. Mean ages of loss of flexion and supination were 2.9yrs and 4.6yrs, respectively. Evolution of supination loss was variable over time. In contrast, flexion loss progressed steadily over time. The pattern of evolution of both flexion and supination was remarkably symmetrical within individuals.

Mean age (proportion of cases; range) at which radiographic features appeared were: IOM 4.1yrs (7/10;0.1-12.4yrs); SUBL 3.6yrs (4/10;1.8-5.2yrs); DISL 5.5yrs (4/10;3.2-6.9yrs); ULNMd 4.2yrs (7/10;0.7-12.5yrs); UBOW15 2.4yrs (3/10;1.5-2.9yrs). Development of radiographic changes was not symmetrical within individuals.

Conclusion:
We present data detailing the natural history of ROM and radiographic changes in the forearm in type V OI. We did not find a close relationship between loss of ROM and radiographic changes in the forearm and elbow.

Take home message:
The symmetry of changes in ROM within individuals with type V OI suggests that these are partially due to intrinsic/systemic factors but not radiographic findings.

OBJECTIVES:
To assess the efficacy and safety of Reflex Locomotion (RL) according to Vojta in the integrated rehabilitation treatment of children with Osteogenesis Imperfecta (OI) both during free-fractures intervals, and after surgery.

METHODS:
In the first study we enrolled 12 OI patients (3.3±2.2 years) with no fractures since at least two months. The rehabilitation program consisted of RL (6 hours/week) and hydrokinesitherapy (2 hours/week) for one month. Outcome measure was the Gross Motor Function Measure-66 (GMFM-66).

In the second study we enrolled 18 OI patients (6.1±2.5) with recent lower limbs long bones fractures treated with intramedullary rodding. We administered RL (7 hours/week) and osteopathic manipulative treatment (OMT) (1 hour/week) for one month. Outcome measures were: pain reduction and standing and ambulation recovery time.

RESULTS:
In the first study, the GMGF-66 significantly improved in each dimension (p=0.03). No trauma events occurred during the rehabilitation interval. In the second study, patients showed a significant pain reduction (VAS:p<0.01 – Friedman test). Mean standing and ambulation recovery times were respectively 26.9± 7.8 days and 31.1±5.6 days.

CONCLUSION:
During free-fractures intervals, even after a relatively short amount of time, OI patients may benefit from RL, without any safety problem. Moreover RL, combined with OMT, proved to be effective also after surgery, ameliorating quality of life and contributing to a good recovery time.

TAKE HOME MESSAGE:
OI, especially in children, requires a global and specific rehabilitation approach, in order to recover the lost gross motor function and to prevent fractures and the worsening of deformities without incurring in traumas during physical therapy. RL according to Vojta, has proven to improve global motricity both after surgery and during free-fractures intervals. Our data showed that RL is safe and it can be associated to other techniques when needed in order to treat OI children with an integrated rehabilitative approach.

P82
Efficacy and safety of Reflex Locomotion in the rehabilitative approach of children with Osteogenesis Imperfecta
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P83
Evaluation of efficacy of oral bisphosphonates (sodium alendronate) therapy in children with mild forms of osteogenesis imperfecta
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Introduction:
Osteogenesis Imperfecta (OI) is a clinically heterogeneous group of diseases related to genetically determined deficiency, or defective collagen structure or collagen gene transcription factors. The most common method of treatment in pediatric population is intravenous administration of bisphosphonates. The usage of oral bisphosphonates in this age group seems to be limited to milder clinical forms and their efficacy is not sufficiently documented.

Objective:
To assess the clinical course of the disease in children with mild OI type (I and IV) and the efficacy of oral alendronate therapy in these patients.

Material and methods:
Based on a retrospective analysis of the medical records of the Metabolic Out-Patient Clinic, clinical data were obtained from 10 children (8 boys) in mean age of 12.58 +/- 4.59 years with clinically mild OI. Mean age of first fracture was 3.64 +/- 2.17 years. Half of them (n = 5; 4 boys) were used for oral bisphosphonate (sodium alendronate) treatment.

Results:
In children treated with bisphosphonates, there was a younger age at the first fracture (3.05 vs. 4.38 years) and had a higher cumulative fracture rate (7.6 vs. 3.8) before therapy. However, these differences were not statistically significant. There was a significant decrease in the incidence of fractures after alendronate treatment (6.2 vs. 1.4, respectively (p<0.01)). None of the patients had any complications. Significant analgesic effects of oral bisphosphonates therapy have also been observed, especially in the subgroup of vertebral compression fractures.

Conclusions:
The analysis confirms the efficacy of oral bisphosphonate therapy in reducing fracture frequency and analgesic effect. This treatment does not appear to be at significant risk for the complications associated with its use in the pediatric population.

Take home message: The oral bisphosphonate therapy have to be considered in children with clinically milder forms of OI, especially with high fractures ratio and bone pain.

P84
Clinical Guidelines for OI, based on an Expert Consensus and Evidence-based Literature
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Objectives
The French Centre of Reference for Skeletal Disorders developed clinical guidelines for Osteogenesis Imperfecta (OI), through evidence review and the consensus of an expert panel of clinicians, geneticists and radiologists.
Methods
The strategy followed the French National Health Authority methodology (www.has-sante.fr/portail/jcms/c_1342513/guide-methodologique-pnds) intended to be used by the Rare Diseases Centers of Reference, to improve the quality and coherence in diagnosis and management of their related conditions.

An initial guidelines draft was created, including statement based upon literature exhaustive review of the last 10 years, and divided in 12 items: clinical and molecular diagnosis with classifications, pharmacological treatments, surgical management, physical and rehabilitation, dental care, pain relief, hearing issues, pregnancy and delivery management, bleeding risk, social and psychological aspects, and inclusive education. The draft was written by a limited working group, then discussed and reviewed by the multidisciplinary reading committee.

Results
Agreement was reached on the 12 chapters. The importance of using imaging tools with low irradiation dose (Spine MRI, EOS imaging, when available) and of minimized frequency of x-rays are emphasized. Adapted physical activity and vitamin D supplementation are the first approaches to optimize bone health. Following the international guidelines, modulation of the bone modeling activity is provided by appropriate bisphosphonates and, in adults, other drugs including anti-RankL antibodies. The Annexes list the Regional OI Centers for diagnosis, management and labelled CPDPN (Centre Pluridisciplinaires de Diagnostic Prénatal). Annexes also include medical protocols, school adaptations tips, card on “home-made immobilization if fracture”, and indicative monitoring timelines by age according to the disease severity (individual risk).

Conclusion
The aim of this concrete document, based on experience and published data, is to have a coherent and common monitoring scheme, adapted for the French Health System from antenatal to adulthood, available for both families, relaying advices and all health providers involved in OI.

P85
Comparison of Pamidronate (PAM) and Zoledronic acid (ZOL) in treatment of children with Osteogenesis Imperfecta
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Introduction:
Osteogenesis Imperfecta (OI) is an inherited disorder with skeletal fragility and is usually caused by mutation in one of the two genes encoding type I collagen (COL1A1, COL1A2).

Cyclic intravenous therapy with bisphosphonates, mainly disodium pamidronate (PAM), has become an established part of the treatment of moderate to severe OI.

Another intravenous third generation bisphosphonates, Zoledronic acid (ZOL), has been used for the treatment of adult osteoporosis.

There is no local data of ZOL therapy in children with OI in Pakistan. This study provide baseline data and will help to guide paediatricians for evaluation and management of OI in children with ZOL.

Objective:
To study the safety and efficacy of ZOL in comparison with PAM, in children with OI.

Methods:
Patients:
n = 32 patients with the diagnosis of OI.,14 patients aged 2-14 years treated with ZOL.18 patients aged 6 months- 12 years treated with PAM.

Treatment protocol:
PAM: was diluted in isotonic saline, administered by slow infusion over 3 hours in a dosage of 1mg/kg/d for 3 consecutive days every 4 monthly.
ZOL: was diluted in isotonic saline, administered IV 0.05mg/ kg over 15 minutes once every 6 months.

Clinical Evaluation:
Patients were followed for clinical and biochemical parameters, side effects, BMD (z-score).

Results:
ZOL group: 14 patients (6 boys and 8 girls) with mean age of 6.28.
PAM group: 18 patients (8 boys and 10 girls) with mean age of 6.
28 fractures were recorded with ZOL group and 32 fractures with PAM group.
Dexa scan showed increased BMD z-score in median lumbar spinal area after treatment with ZOL.
Infusion of ZOL was associated with less hypocalcemia.

Conclusion:
ZOL is an effective mode of treatment as compare to PAM with less side effects. Less no. of infusion
The treatment response is comparable to PAM

P86
Prevalence and Treatment of OI-Related Hearing Loss with Bisphosphonates
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POURPOSE:
Osteogenesis Imperfecta (OI) is a bone disorder that stems from a mutation in type 1 collagen genes. The prevalence of hearing loss in OI varies from 50-92%. Bisphosphonates limit bone turnover and are used to treat OI. Recent research suggests bisphosphonates can halt the progression of OI-related hearing loss.

METHODS:
Retrospective review of 133 OI patient charts identified 13 patients (ages 9-69) with audiograms. Pure tone averages of patients with a single audiogram (N=9) were reviewed in the context of their age, OI type, and bisphosphonate treatment. PTAs of patients with more than one audiogram (N=4) were analyzed longitudinally with bisphosphonate treatment (hearing loss defined as ±10dB since previous audiogram).

RESULTS:
12/133 patients were not given an audiogram by an ENT. 13/133 patients had an audiogram. 6/13 patients did not experience hearing loss, 3 of which took bisphosphonates. 7/13 patients with audiograms displayed hearing loss, 5 of which were treated with bisphosphonates. However, only 1 patient was diagnosed with hearing loss, OI Type I, and treated with bisphosphonates. 2 OI Type I patients with hearing loss never took bisphosphonates. All patients with hearing loss were over the age of 18.

CONCLUSION:
The comparisons made in this study suggest that the use of bisphosphonates in patients with OI is equivocal in halting the progression of hearing loss. Because most patients did not have multiple audiograms, it is difficult to postulate whether bisphosphonates have decreased deterioration of hearing loss. These results also demonstrate the need for communication between specialists to optimize OI care and the lack of patient compliance in following physician recommendations.

SIGNIFICANCE:
Hearing loss may potentially be averted and/or the progression halted with bisphosphonate use. Emphasis needs to be placed on getting regular hearing tests so that proper treatment can be administered and its effects observed.

P87
Vitamin D level as additional risk factor for osteoporosis in children with OI
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To evaluate additional risk factors for osteoporosis in OI patients, 198 children were hospitalized in Center of Inborn Pathology in 2011 - 2017.

Serum concentration of 25-hydroxyvitamin D (25OHD3) was measured in 145 children (44 girls), age from 2 months to 17 years.

At baseline, the average serum 25OHD3 concentration was 50.6 ng/ml (SD 20.6).
Decreased level of vitamin D (<30 ng/ml) was found in majority of patients with OI (64%).

However, 5% of patients (all under 24 months), had toxic level of vitamin D (more than 100 ng/ml). All patients were treated with bisphosphonates. Additionally, patients with decreased vitamin D level received vitamin D3 supplementation in the dose 2000-6000 IU, depending from the baseline vitamin D3 level, season, latitude and access to sunlight.

Vitamin D supplementation was associated with higher serum 25OHD concentrations in 88% of children. Increase of lumbar BMD after two years of combined treatment with bisphosphonates and vitamin D was noted in 97% of patients.

Conclusion:
Abnormal vitamin D level is often finding in OI patients. Vitamin D supplementation in the dose 2000-6000 IU in combination with bisphosphonates treatment causes increase in serum 25(OH)D3 concentration and bone density.

P88
Adults with Osteogenesis Imperfecta in the Netherlands: clinical characteristics of 151 patients
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Objective
In 2007 an expert center for adults with Osteogenesis Imperfecta (OI) was founded at the Isala Hospital in Zwolle, the Netherlands to achieve optimal care for adult people with OI. This observational follow-up study provides an overview of clinical characteristics of the patients who visited the clinic during its first 5 years. The focus is on bisphosphonate use and bone density measurements at time of presentation at the expert center.

Methods
Clinical data such as patient history, DEXA measurements and laboratory data are, with patient consent, collected during their first visit.

Results
A few remarkable results are as follows:
• 24/124 (19%) had a 25OH-vitamin D levels <50 nm/L at their first visit. A small group reported consuming calcium and vitamin D supplements
• Men with OI type 1 aged <50 years had significantly lower Z-scores of the lumbar spine compared to women.
• Both T and Z scores were considerably lower when measured at the LS compared with the measurement of the PF in type 1 and 4 patients.
• Bisphosphonate use is variable in adults with OI. In patients with OI type 1, 3 and 4 respectively 47.6%, 27.8% and 59.1% had never used bisphosphonates.
• Occurrence of osteonecrosis in the jaw and atypical femoral shaft fractures is being analysed in this group of OI patients.

Conclusion
By describing clinical data of a large group of adults with OI a clinical picture of the adult patient with OI type 1, 3, 4 emerges.

Take home message:
The setting of care for adults with OI in a national expert center and registry of data in one single database, allows exploration of many important aspects and questions in the future regarding OI over time, for example the efficacy of BP treatment in adults with OI in terms of BMD and fracture incidence.

P89
LONG-TERM EFFECT OF ZOLEDRONIC ACID TREATMENT ON BONE MINERAL DENSITY IN ADULT PATIENTS WITH OSTEogeneSIS IMPerFECTA (O1).
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CONCLUSIONS:
Ziv treatment improves spine BMD, regardless of the previous use of bisphosphonates. Long-term benefits in the femoral neck are not clear.

P90
Patients with Osteogenesis Imperfecta in the emergency department, the need for extended trauma screening and assessment

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Objectives
We report four patients with Osteogenesis Imperfecta (OI) who sustained severe injuries after low impact traumas. The aim of these case histories is to underline the importance of extended trauma screening of patients with OI.

Methods
Four case histories were assembled from patients who sustained injuries after low impact traumas.

Results
Patient 1, OI type 3, 26 years old. He fell forwards with his wheelchair. Trauma screening identified an adequate and cooperative patient with a hematoma under the right eye and a bilateral tibia fracture. He became unwell and a cerebral CAT scan showed an impression fracture of the frontal and maxillary sinuses with a subdural hematoma, which caused his death.

Patient 2, OI type 1, 21 years old. She fell from her bike and was diagnosed with a clavicle fracture. A cerebral CAT was performed which showed a fracture of the zygomatic bone the maxillary sinus and an orbital fracture. Surgical treatment was necessary.

Patient 3, OI type 3, 29 years old. This patient was a refugee and had several falls during his journey. Since the last fall he had constant neck pain. A CAT-total body was performed. Multiple recent fractures including an odontoid fracture, were observed.

Patient 4, OI type 3, 36 years old. He fell out of his wheelchair. Trauma screening (including a cerebral

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**OBJECTIVE:**
To evaluate evolution of bone mineral density (BMD) values after treatment with intravenous zoledronic acid (Ziv) in adult patients with (OI).

**MATERIAL AND METHODS:**
A retrospective study. All patients received calcium and D vitamin supplements. A dose of 4 mg Ziv was given every 12 +/- 6 months. Student t-test for paired samples was used after verification of the normality assumption using the Shapiro-Wilk test. Fisher-Pitman test for paired samples was used if not met.

**RESULTS:**
20 patients (70% women) with 35.2 years (SD: 11.5) were treated. Median follow-up was 5.5 years (RI: 5.5). 5-year densitometric data are available in 50% of patients. 65% of patients (n = 13) received other bisphosphonates prior treatment. Mean BMD at baseline in spine (L1-L4) and femoral neck was 0.741 g/cm² (SD: 0.178) and 0.665 g/cm² (SD: 0.174) respectively. Mean percentage change in spine from baseline after 3 years (n=12) and 5 years (n=10) of treatment was +6.73% (SD: 9.0) and +10.5% (SD: 12.1) respectively. Mean percentage change in femoral neck from baseline after 3 years (n=12) and 5 years (n=10) of treatment was +13.2% (SD: 18.4) and -2.0% (SD: 17.5) respectively. Compared with baseline values, after 3 years of treatment, patients presented statistically superior BMD values in both the spine (p = 0.02) and the femoral neck (p = 0.01). After 5 years spine values remained significantly higher than those obtained at 3 years (p = 0.03) while femoral neck values were significantly lower. Results are independent of the previous bisphosphonates use, except for femoral neck after 5 years of treatment.
CAT) showed multiple fractures of his left arm and a parietal fracture including an epidural hematoma.

Conclusion
Patients with OI should have further trauma screening after low energy trauma and there should be a low threshold for further investigations, such as a cranial CAT-scan or a total body CAT scan.

Take home message:
Screen an OI patient with a reported low energy trauma as if it concerned a high energy trauma.

P91
Osteogenesis Imperfecta in Lombardy
Guide Lines for diagnosis, treatment and rehabilitation from childhood to adult.
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Objectives:
Osteogenesis imperfecta (OI) is the most common bone genetic disorder and it is characterized by bone brittleness and various degrees of growth disorder. Clinical severity varies widely and nowadays eight types are distinguished. A multidisciplinary approach has been established in Italy since the last 30 years. For simplicity, the objectives of treatment can be reduced to three typical situations: the lethal perinatal form, in which the problem is survival at birth; the severe and moderate forms, in which the objective is ‘autonomy’; the mild form, in which the aim is to reach ‘normal life’.

Methods:
Three types of treatment are available: non-surgical management (physical therapy, rehabilitation, bracing and splinting), surgical management (intramedullary rod positioning, spinal and basilar impression surgery) and medical management (drugs to increase the strength of bone and decrease the number of fractures as bisphosphonates or growth hormone, depending on the type of OI).

Results:
Suggestions and guidelines for therapeutic approach are indicated, updated with the most recent findings in OI diagnosis and treatment.

OI diagnosis is usually made by experts, through clinical and radiological basis, BMD and DNA analysis. The plan of care involves patient, family, medical and nursing staff, and community. Rehabilitative approach following intramedullary telescopic roding has been shown to improve walking capability. Surgical treatment in patients with progressive spinal deformity and in those with basilar impression is useful in decreasing the rate of complication.

Surgical, medical and rehabilitative program for adults has been discussed. In lack of significative international guidelines the working group has pointed out a few points of agreement.

Conclusion:
The objective of therapy should be to provide the maximum long term function and autonomy that the disease allows.

Take Home message:
A multidisciplinary team approach is essential for diagnosis and communication with patient and parents.

P92
Sclerostin antibody effects in xenograft model using bone harvested from pediatric OI patients
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Ferrous Ward, Student, University of Michigan, Ann Arbor, United States of America;
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OBJECTIVE
Sclerostin antibody (SclAb) is under consideration as a bone forming treatment for OI. A recent clinical trial supports use in adults, yet cellular response to therapy has been limited to mouse models. Furthermore, the effects of SclAb across OI type and severity remain unknown. The purpose of this
P93  
Dental implants in patients with osteogenesis imperfecta: a 6-year follow-up study

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Objective:
The objective of the present study was to follow up a primary prospective study reporting high implant survival in a group of Norwegian patients with osteogenesis imperfecta (OI). Our hypothesis was that implant treatment in these patients has approximately the same long-term success rate as in healthy persons.

Methods:
The primary study included seven patients (20 implants), of whom four patients (11 implants) agreed to participate in the present study, three patients had died. The patients were initially examined after an average of 19 months (range 11-26 months) and followed up after an average of 93 months (range 91-109 months), subsequent to prosthetic loading. The implants were clinically and radiographically examined and the patients were requested to subjectively evaluate the implant treatment. A visual analogue scale ranging from 0 as the worst to 10 as the best score was used.

Results:
At the primary study, no implants were lost and only 1 mm bone loss was registered around two implants in one patient. One implant was removed after 76 months due to an implant neck fracture, unrelated to disease. At the follow-up study, 4 mm bone loss was observed around two implants. Four implants showed only 1 mm bone loss, two of which had the same level of bone loss at the primary study. No bone loss was detected around the remaining four implants. Subjective and objective evaluation of implant treatment,
respectively, showed overall satisfaction of 9.9/10 and 9.1/10 after the follow-up study.

Conclusion:
The long-term follow-up study indicated that implant survival rate and patient satisfaction towards implant treatment were fairly high in these patients.

Take home message:
Dental implant treatment has a relatively high success rate in patients with OI.

P94
Effect of Bisphosphonates and Denosumab on trabecular bone: A pilot study in children with Osteogenesis imperfecta
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Objectives
Osteogenesis imperfecta (OI) is a hereditary connective tissue disorder due to mutations related to collagen type 1. OI therefore presents itself with low bone mass, resulting in high bone fragility. Although bisphosphonate treatment is able to increase areal bone mineral density (aBMD) measured by DXA, there is no correlation to fracture rates. The aim of this study was to retrospectively analyse the trabecular bone score (TBS) in children with OI, who were treated with bisphosphonates during one year and with denosumab during the following year. TBS, already used in adults with osteoporosis, is supposed to represent the cancellous bone and by that the stability of the bone more accurately than aBMD.

Methods
3 DXA scans (GE lunar iDXA, lumbar spine) of 8 children with OI were performed at intervals of 12 months each. The first 2 scans were carried out during bisphosphonate treatment. The last was performed after 1 year of denosumab treatment. Paediatric TBS assessment was performed with a custom version of TBS iNsight (Med-Imaps SASU, France). TBS and BMD variations were expressed in % from baseline and normalized at 12 and 24 months.

Results
DXA assessment showed an increase in aBMD of about 6,2%/25,1% after 12/24 months. TBS showed an increase of 2,1/6,6%. In single case analysis there were differences between trends of aBMD and TBS. Age related standard deviation for TBS increased significantly under denosumab treatment, but not under bisphosphonate treatment.

Conclusion
In our pilot trial no correlations between TBS and DXA parameters have been observed. The significant lower increase of TBS demonstrates a stronger effect of antiresorptive drugs on cortical than trabecular bone.

<<Take home message>>
TBS can differentiate between trabecular and cortical bone and can provide a better understanding of bone response to different treatment strategies.

P96
Is raised platelet count an indicator of an inflammatory process in osteogenesis imperfecta?
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Background
Platelet count has been observed to be a marker of inflammation in a variety of settings including cancer, auto-immunity and inflammation with intercurrent illness. We noticed raised platelet counts in children with osteogenesis imperfecta (OI) attending the Sheffield metabolic bone disease service for treatment. We decided to systematically assess the occurrence of above average or raised platelet counts as a potential marker of inflammation.

Methods
We reviewed the Sheffield Children’s Hospital records of 71 children. All fulfilled the criteria necessary to be included in the nationally-funded
Highly Specialised Severe, Complex and Atypical OI Service. These criteria include multiple early life fractures; 6 or more vertebral crush fractures; multiple rodning or Ilizarov surgery of limbs; intractable bone pain; cranio-cervical, skull base or spine deformity requiring surgery; or unusual (non-collagen gene) forms of OI.

Data were extracted from hospital notes, digital radiology records and the pathology database; variable length records relating platelet count (below/average, above upper limit) to prior and intercurrent events were summarised as event proportions per child, collated into a rectangular dataset, then analysed using standard statistical techniques in DataDesk 7.0.2.

Results
49 of 71 patients had at least one platelet count above the normal range. The mean±SD proportion of platelet counts below average, above average and within the normal range, and above the age and sex-related normal ranges by patient are shown in the table below in relation to potential confounding/explanatory factors.

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<td>New vert#</td>
<td>Existing vert#</td>
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<tr>
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<td>Surgery</td>
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<tr>
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</tr>
<tr>
<td>0.04±0.10</td>
<td>0.15±0.24</td>
<td></td>
</tr>
</tbody>
</table>

a: p<0.05; b: p<0.0001 for Student’s t-test of plts>ULN vs plts≤avange

Conclusions
Raised platelet counts were observed in association with new and healing fractures, but also (41%) in the absence of defined pro-inflammatory factors or events.

Take home message
We speculate that these findings are evidence for a pro-inflammatory component to OI that could be a target for therapeutic intervention

P97
Biological Networks Application: In Silico Analysis of the Roles of the Related Functional Genes and Pathways in Osteogenesis Imperfecta
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Objectives:
Osteogenesis Imperfecta (OI) is a genetic disorder with the skeletal and connective tissue defects. Mutations, deletions/duplications in the genes of biosynthesis, post-translational modification, processing of collagen type 1, and also osteoblasts differentiation are the causes of OI. The aim of our study was to construct a network of the related genes, proteins, and the pathways involved in OI. The platform of the functional genomics and proteomics might open up a new window to interpret the genes and proteins associations in OI.

Methods:
A network of the genes was applied to perform a comprehensive literature review to discover the genes and the pathways involved in the pathogenicity of OI. BioLab Experiment Assistant (BEA) application (http:// www.biovista.com) based on integrated system literature analysis was used to construct the gene-pathway network. STRING database with special algorithm was also applied to visualize the protein-protein interaction network and find the impact of important genes of OI.

Results:
Our study presented a platform of the interactions of the functional genes and pathways related with OI. Furthermore, those with a role in the ossification process,such as bone development and resorption, collagen biosynthesis, dentinogenesis, and etc. could be categorized. COLLAGEN, COL1A1, COL1A2, COL3A1, CRTAP, CALCITONIN, OSTEOCALCIN and LEPRE1 and some others were found to be the proteins of importance in the
pathways leading to OI. The STRING data also confirmed the interactions of several functional proteins which might cooperate with each other in the specific biological networks (P-value<0.05).

Conclusion:
The database provided by our study is based on system literature analysis for rapid search of association between genes and biological pathways in OI. This might open up the new windows to OI treatment by modulating the interactions of the key proteins. Novel drug discovery against OI might be also the potential outcome of the introduced network application.
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