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MEETING REPORT

6th International Conference on Children's Bone Health

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Meeting report from the 6th International Conference on Children's Bone Health, Rotterdam, Netherlands, 22-25 June 2013

With 306 delegates from 45 countries from around the world representing more than a dozen specialities, and with a total of 271 presentations of invited talks, abstract presentations and both oral-poster and poster-board presentations, the meeting covered a wide range of science and medicine related to 'pediatric bone'. We present a summary by day of the highlights but encourage all the readers of *BoneKEy* to look at www.iccbh.org to fully appreciate the program, and, for further information, enroll in the mailing list at iccbh@ectsoc.org. We thank the ECTS for its high level of organizational support and the IBMS and ASBMR, in addition to the ECTS, for additional Society support that allowed our meeting to be so successful. We thank our commercial sponsors Alexion Pharmaceuticals Inc., Danone, Novartis, Novotec/Stratec and UCB for their unrestricted educational grants as well.

Our meeting began with a Training Course on Saturday, in an effort to promote younger attendees having a broad view of our field. *Nick Bishop* (Sheffield) opined on what a basic bone scientist needs to know about clinical bone disease, emphasizing the importance of the phenotypes of bone fragility (osteogenesis imperfecta, idiopathic juvenile osteoporosis), bone deformation (using examples of rickets, dysplasia and osteolysis) and high bone mass (various forms of osteopetrosis), patient-centered outcomes for successful therapy (freedom from fracture, improvement or delay in deformity and replacement of defective bone) and the integration of basic science discovery into rationale drug design (reviewing possible approaches to excess FGF23-based diseases). As counterpoint, this was followed by *Harald Jüppner* (Boston) discussing what a clinical bone scientist needs to know about basic bone biology, in which he stressed pathways for signaling in bone (interactions of osteoblast and osteoclast through RANKL and OPG), the role of the osteocytes as a mechanosensor and a chemical sensor for integration of bone remodeling, whole-exome sequencing and subhuman models of bone disease involving the PTH/PTHrP receptor knockout mice that are available. The two talks complemented each other nicely and led to a discussion in the next session to two hot topics in bone. The first comprised the area of hypogonadal bone disease in adolescents, where *Wolfgang Högler* (Birmingham) presented new data on the roles of sex steroids in bone in humans and some experimental models and *Annamieke Boot* (Groningen) discussed the triad-athlete female individual in relation to this topic, the obese child, the effects of anti-psychotic medications on bone and the child with cerebral palsy who needs management of menstruation, among others. Both stressed the issues of bone development in the environment of sex steroid appearance and the effects of not having normal activity as a precipitating factor to fractures. The second directed session discussed the exploding biology of phosphate homeostasis in relation to bone disease. The mechanisms whereby we conserve phosphate were presented by *Farzana Perwad* (San Francisco), stressing the tight integration of FGF23 and its recent biology of post-translational processing, and the specific dysfunctions of the system were discussed by presentation of three relevant cases by *Rachel Gafni* (Bethesda) involving FGF23, which revolved around the disorders of X-linked hypophosphatemic rickets, fibrous dysplasia and hereditary familial tumoral calcinosis. Immediately thereafter, the opening address of the meeting was given by *Francis Glorieux* (Montreal) where osteogenesis imperfecta was used as a disease model to review bone biology and its expression in humans, tying together the entire Training Course thesis, whereby understanding one aspect leads to the other and vice-versa.

Sunday was focused on two main topics: epidemiology and biology of the fracturing child and rare bone diseases. Although fractures are viewed as a not-uncommon event in children (one out of three healthy children sustains a fracture, mainly, of the forearm), children with fractures may have underlying abnormalities of bone that warrant prevention, evaluation and potential therapies. According to *Emma Clark* (Bristol), there is good evidence from prospective and case–control studies that

low bone density is a risk factor for fractures not only in adults but also in children. Moreover, there is increasing evidence that other factors (obesity, ethnicity and physical activity) contribute in increasing the risk of fractures through their influence on bone density and bone size. *Kassim Javaid* (Oxford) presented longitudinal data demonstrating that maternal environment and nutrition influence not only neonatal bone density and size but also their trajectories in later life and consequently the risk of fractures throughout the life cycle. Recent advances in bone imaging (mainly, high-resolution pQCT) now allow performance 'virtual non-invasive bone biopsies' of distal radius and tibia. *Salman Kirmani* (Rochester) reported that HR-pQCT has revealed a transient increased cortical porosity, with a consequent reduced cortical strength, during the pubertal growth spurt, which may explain the peak incidence of forearm fractures at this time. The comparison of children with or without distal forearm fractures due to mild trauma has shown cortical thinning and reduced trabecular microstructure in boys and girls with fractures. In a special group of patients, children affected by chronic kidney disease (CKD), *Kate Wesseling-Perry* (Los Angeles) confirmed the importance of traditional bone biopsy to understand changes in bone turnover, mineralization and volume. After the recent observation that the bone expression of FGF23 (fibroblast growth factor 23), DMP1 (dentin matrix protein 1) and sclerostin (SOST) is linked to skeletal-mineralization abnormalities in children with CKD, osteocytes are now considered endowed with endocrine activity. Several oral communications from the submitted abstracts presented new data on different risk factors for fractures in children: Thandrayen demonstrated that maternal concordance in South African adolescents with fractures is present across different ethnic groups. Medina-Gomez reported that ethnic differences in bone density are evident since early childhood and are linked to difference in skeletal size and adaptation to loading (lean mass). Finally, Moon demonstrated that maternal 25-OH vitamin D levels are associated with hand grip strength and the percentage of lean mass of the child (studied at 4 years of age).

Regarding rare diseases, *Agnes Linglart* (Paris) summarized the recent advances in the genetics and pathogenesis of acrodysostosis, a rare chondrodysplasia. According to these observations, the disease is caused by deficient action of PTHrp. Moreover, the two main heterozygous mutations have different impact on hormones: patients with *PRKAR1A* mutation have resistance to hormones acting through G-protein receptor signals (PTH and TSH), whereas patients with *PDE4D* mutation do not show such hormone resistance. *Maja Di Rocco* (Genoa) presented an overview on the numerous skeletal manifestations observed in Gaucher's disease (a lysosomal storage disease). Recently, reduced bone density was found to result not only from increased osteoclast activity but also from osteoblast dysfunction due to glycolipid accumulation and from an altered signaling from osteoclasts to osteoblasts, due to the decreased production of sphingosine 1 phosphate. Specific enzyme therapy, although effective in significantly improving other organ alterations, produces only a slow and partial improvement of bone complications. *Gerard Pals* (Amsterdam) summarized the recent observations regarding the known mutations in collagen type I genes in osteogenesis imperfecta (OI), both traditional ones, COL1A1 and COL1A2, and those newly discovered. However, 25% of over 1200 OI cases studied at his laboratory were not found to have any known mutation, which means that additional gene mutations for OI are still to be identified. Some communications presented new animal models for some rare diseases. Del Fattore and colleagues developed the first animal model of autosomal dominant type II osteopetrosis. Vogiatzi presented a study on *th3*/+ thalassemic mice to investigate the role of erythropoietin and hematopoietic progenitors in thalassemia and their consequences on osteogenesis. Finally, Trichet discussed the possibility to use a lentivirus-delivered shRNA to improve collagen quality in OI. Such animal studies are very important to better evaluate the penetrance and the pathogenesis of the diseases and to develop and evaluate novel and targeted therapies.

Finally, the Sunday evening Symposium further expanded the 'rare diseases' topic by discussing unusual forms of rickets and hypercalcemia and their differential diagnosis: *Martin Konrad* (Munster) discussed a newly discovered molecular etiology of idiopathic infantile hypercalcemia (systemic 24-OHase deficiency), *Harald Jüppner* (Boston) discussed the role of the PTH/PTHrp receptor mutations, including Jansen's metaphyseal chondrodysplasia, Eiken familial skeletal dysplasia, Ollier's disease, and *Nick Bishop* (Sheffield) discussed the biology and human manifestations of hypophosphatasia and an exciting replacement enzyme in advanced stages of clinical trials.

The Monday sessions focused on 'The Fracturing Child', starting with *Mary Leonard* (Philadelphia) and *Judith Adams* (Manchester) discussing the use of imaging modalities and their current limitations. Although DXA remains the most widely used imaging modality in both adults and children for the assessment of bone mass, it is clear that the ability of DXA to predict fracture risk in an individual child is poor. Modalities that provide assessment of compartment-specific bone density and architecture are not so widely available and have limited applicability in younger children because of the prolonged scan times. The therapeutic approach to a child with fragile bones is a multidisciplinary one in most cases, reflecting either the complexity of the management of more severely affected children with osteogenesis imperfecta (the largest group) or the need to manage underlying conditions characterized by inflammation or immobilization. Bisphosphonates remain the mainstay of treatment in many situations, but the additional benefits of good nutrition including vitamin D and physical activity were emphasized. Lectures by *Craig Munns* (Sydney) and *Catherine Gordon* (Providence) provided delegates with a clear view of the state of the art. The oral communications in the first morning session reflected the fractures and fragility theme; those in the second session were more of a mixture but with a continuing emphasis on therapeutic intervention. The continuing sessions invited speakers who reminded delegates of the burden of bone disease in inflammatory bowel disease, particularly in those with Crohn's (*Susanne Schmidt*, Gothenburg), and diabetes (*Susanne Bechtold*, Munich) and the importance of the interaction between muscle and bone in determining bone strength and structure (*Frank Rauch*, Montreal). The intricacies of the interactions between disease and tissue—glycation of collagen cross-links leading to altered material properties in diabetes, for example—were nicely balanced with the organ-level interaction showing function-determining structure across the whole tissue. The oral communications covered a variety of chronic diseases with a clear pattern of focus on spine outcomes, both in terms of

vertebral fracture and overall spine shape. Monday ended with a symposium focusing on vitamin D. Speakers (*Zulf Mughal*, Manchester; *Mairead Kiely*, Cork; *Catherine Gordon*, Providence) provided clear messages concerning the need to be vigilant with respect to vitamin D deficiency at times of rapid growth and in situations where calcium intake was limited. The current state of play with respect to supplementation as opposed to food fortification was hotly debated, and delegates had to continue their discussions onto the lovely boat-based social event.

Our Tuesday half-day session started with travel awards to over two dozen young investigators who presented their work at the meeting, the Slemenda award to Maria Luisa-Bianchi (Milan), and was followed by two late-breaking abstracts: Trabecular bone score (TBS) extracts a texture parameter from pixel gray-level variations in DXA lumbar spine images. Its use with DXA-based values, to approximate microarchitectural findings in young adolescents, was presented by Winzerieth, who suggested age-related TBS curve can be useful, in complement to the BMD curve, to help clinician to identify children with bone microarchitectural modifications induced by chronic diseases or drug therapies. We await such studies in the future with great anticipation. The recently discovered mutation of WNT1 signaling in a family characterized by both osteoporosis and seemingly OI was presented by Mäkitie who broadened her discovery to help us understand the complex clinical spectrum of bone loss. We ended the 6th ICCBH Conference with two 'Round Table Sessions' on the important topics of Pediatric Cancer and Bone, and Obesity as a Bone Disease. Together with substantial improvements in survival in childhood cancer, and due in part, to newer therapeutic agents, bone loss and/or avascular necrosis occur not infrequently in the survivors. Both are caused by a multitude of factors. Data on the clinical impact of treatment and prevention of the later aging skeleton are forthcoming as well. *Carmen Wilson* (Memphis) discussed two cancer survivor studies from the United States, whereas *Marry van den Heuvel-Eibrink* (Rotterdam) discussed the relevance of searching for single-nucleotide polymorphisms (SNPs) for these skeletal complications. *Paul Baldock* (Sydney) presented the thesis that energy and bone homeostasis is linked but is far more complex than a response to weight bearing. This system has many levels of control, involving both centrally mediated and direct-signaling pathways. Osteocalcin emerged as a candidate for feedback signaling. Skeletal changes to assess the impact of obesity on children's bone health cannot be captured by DXA alone, and the use of HRpQCT and microMRI may help to overcome these limitations (*Paul Dimitri*, Sheffield). Especially during puberty, skeletal changes may be most apparent. Further strategies for optimizing peak bone mass and for prevention of fractures across all ages are needed clearly.

Conflict of Interest

The authors declare no conflict of interest.