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MEETING REPORT

News on bone metabolism and bone density in health and diseases during growing age: ECTS 2012

This article has been corrected since Online Publication and a corrigendum has also been published

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At the ECTS Congress recently held in Stockholm, many communications in both basic and clinical sessions were focused on bone metabolism in health and disease during the growing age. This is a short report on some novel insights in the pathogenesis or treatment of rare diseases and on some other 'hot' topics still under discussion and requiring special attention.

The reappearance of nutritional rickets in developed, and even sunny, countries has been known for several years, but is still often neglected. This was underlined by Karras *et al.*,[1] who observed a high incidence of vitamin-D deficiency in mothers (82.3%) and neonates (62.5%) in a region of Northern Greece. Thomsen *et al.*,[2] in a study on 107 women and their children, found that maternal 25-OH D-status at delivery was the main determinant of infant 25-OH D-status even 9 months after birth. Maternal 25-OH D-levels >50 nmol l^{-1} are required to avoid infant deficiency. Low 25-OH D-levels at birth were associated with impaired growth during the first 9 months of life. This confirmed the epidemiological data and prospective studies showing that maternal vitamin-D levels are important for healthy bone density accrual in children, not only during the first months of life but throughout infancy. Vitamin-D supplementation during pregnancy remains controversial, but a randomized trial by Hollis[3] showed that 4000 IU per day of vitamin D in pregnant women are safe and effective in achieving sufficiency in mothers and neonates, regardless of race. Hollis[3] also reported that in a group of 350 women receiving different daily doses of vitamin D (400, 2000 or 4000 IU) during the last 6 months of pregnancy, those receiving the higher doses had less pregnancy-related morbidities, such as preeclampsia, eclampsia or gestational hypertension. More studies are of course needed to translate these findings in general practice. Vitamin-D assessment, particularly in children, might become easier and cheaper if the preliminary results of a newly adapted enzyme immunoassay that measures vitamin D on spot urine samples[4] will be confirmed in a larger population.

The importance of physical activity (PA) for bone has been the subject of several communications. Regular moderate to vigorous PA is associated with greater bone strength and density during childhood and adolescence, but its relevance for bone health in the long term is still controversial. A Swedish study[5] showed that PA in younger years was associated with a lower risk of sustaining a fracture. Comparing 709 former male athletes (median age 70 years; regular sport activity ceased for a median of 35 years) with 1368 controls, the authors observed a lower risk of sustaining any fracture, any fragility fracture and distal radius fractures in the former athletes, even if, after age 50 years, the difference was not statistically significant for hip fractures. To demonstrate that PA in early youth can reduce the incidence of fragility fractures in the elderly age would be extremely important to design strategies aimed at reducing osteoporotic fractures.

As expected, the most interesting news regarded the pathogenesis and treatment of bone alterations in rare diseases.

Hypophosphatasia (HPP), a disease characterized by defective bone and tooth mineralization, is due to a deficiency of tissue non-specific alkaline phosphatase (TNSALP), caused by a loss-of-function mutation. HPP is probably under-diagnosed, as bone specialists are mainly focused on the problem of increased ALP levels. Enzyme-replacement therapy with a bone-targeted recombinant TNSALP (ENB-0040) is currently being studied. ENB-0040 has been shown to prevent HPP manifestations in *TNSALP* knockout mice and clinical trials are ongoing. Arundel[6] presented preliminary data showing significant improvements in rickets and respiratory status after 12 months of ENB-0040 therapy in a small number of infants and young children with severe HPP. Whyte *et al.*[7] presented the results of ENB-0040 therapy on 6 adolescents and 13 adults with HPP, demonstrating significantly decreased TNSALP substrates and improved physical performance (measured by the 6-min walk test). The availability of an effective, specific therapy for HPP would be

an important advancement, as two surveys on 184 patients (59 children and 125 adults)[8] clearly documented the impact of HPP on life quality. Overall, 58% of these patients reported at least one fracture. The 125 adults sustained a mean of 13.9 fractures (range 1–100), and 98% of those with adult-onset HPP sustained at least 1 fracture (mean 11 fractures): 75% of fractures were at lower limbs and disability was a common consequence. Regarding the animal models of HPP, Mentrup *et al.*[9] presented the first mouse model with a dominant-negative *TNSALP* mutation.

Osteogenesis imperfecta (OI) is certainly one of the most studied rare diseases, and interesting new data were presented. Chappard *et al.*[10] evaluated the effects of sclerostin antibody (Scl-Ab) on the trabecular axial skeleton fracture rate, and on the lumbar vertebral body bone mineral density and micro-architecture, in oim/oim mice, an established model of OI type III. With Scl-Ab treatment, bone mass and connectivity of the lumbar vertebral trabecular network increased, which explained the reduction in fracture rate. Hopefully, Scl-Ab might become a therapy for human OI type III, the most severe form of OI. New findings were also presented for OI type I, a mild form characterized by mutations leading to either a decreased amount of normal collagen (quantitative mutation) or structurally aberrant collagen (qualitative mutation);[11] the study of mineral crystal size performed on bone biopsies from children affected by OI type I indicated the probable occurrence of a common bone cell defect, downstream from both quantitative and qualitative collagen mutations.

Two other studies on rare diseases deserve special mention. A study on infantile malignant osteopetrosis (IMO)[12] raised hopes of a possible gene therapy of this lethal disease and other diseases involving osteoclasts, presenting the first *in vitro* evidence of lentiviral-mediated genetic correction. More than 50% of IMO patients have mutations in the *TCIRG1* gene; in this study, *TCIRG1*-corrected osteoclasts showed bone resorption activity, releasing increased $Ca2+$ and bone degradation products (CTX-1) into the media and forming resorption pits on bone slices, whereas non-corrected IMO osteoclasts developed normally but failed to resorb bone. Another study involved a very rare disease (gerodermia osteodysplastica, GO), an autosomal recessive progeroid syndrome characterized by precocious ageing, including osteoporosis in infancy. GO is caused by loss-of-function mutations in a Golgi protein (Gorab) of unknown function, expressed in osteoblasts at higher levels than in osteoclasts. The authors studied mesenchymal cells of the long bones in affected animals and observed impaired function and differentiation of early osteoblasts, a possible mechanism leading to osteoporosis in GO.[13]

Bone cancer was another important topic, considering that osteosarcoma (OS) is a frequent pediatric neoplasm. RUNX2, a master regulator of osteoblast differentiation and suppressor of proliferation, is aberrantly expressed in OS, and may support OS cell growth. Taipaleenmaki *et al.*,[14] studying the possible contribution of microRNAs (miRNAs) to modulations in RUNX2 levels, discovered that elevated RUNX2 protein expression is directly linked to diminished expression of several RUNX2 targeting miRNAs. In particular, the p53-dependent miR-34c was shown to be an integral part of a novel regulatory network that controls proliferation of bone cells and is compromised in OS.

Finally, there were new preliminary observations from growth plate studies. It is well known that growth-plate cartilage is responsible for bone lengthening during growth, but many mechanisms of this process are still incompletely elucidated. *C2orf82* is a novel gene encoding a small type I transmembrane protein (C2ORF82), expressed exclusively in the proliferating and pre-hyperthrophic chondrocytes of all long bones. Moffatt *et al.*[15] presented preliminary data on *C2orf82* global knockout mice, which showed mild but significant reduction in bone length. The results suggested that C2ORF82 is a novel transmembrane chondroitin sulfate proteoglycan that regulates chondrocyte differentiation and bone growth. Another study by Wong *et al.*[16] suggested that Wnt-β-catenin signaling stimulates osteoblast differentiation and suppresses chondrogenic differentiation during repair of an injured growth plate, which could explain why a damaged growth plate is often inappropriately repaired by bony tissue. Intervention on Wnt-β-catenin signaling might represent a potential approach in enhancing cartilage regeneration after growth-plate injury. Another study[17] evaluated the mechanisms involved in chondrocyte hypertrophy, the main process responsible for bone elongation, in postnatal mouse metatarsal explants cultured in presence of autophagy inhibitors. All inhibitors significantly promoted bone growth, with enhanced chondrocyte differentiation and marked increase in cell size, thus suggesting that inhibition of autophagy promotes chondrocyte differentiation and longitudinal bone growth. Finally, an interesting study showed the possible influence of anti-epileptic drugs (AEDs) on the growth of cartilage. Considering the wide use of AEDs in growing subjects, their possible impact not only on bone but also on cartilage may have a relevant influence on skeletal development. Culturing articular chondrocytes of healthy male rats in the presence of different AEDs (valproic acid, VPA; oxcarbazepine; levetiracetam; lamotrigen; topiramate), Wang *et al.*[18] observed that all these drugs inhibited chondrocyte growth. VPA caused the most significant inhibition, and its intra-articular injection *in vivo* resulted in increased cell death. These results strongly suggest that articular cartilage conditions should be monitored in epileptic children and adolescents on AED treatment.

New exciting developments in this dynamic field will certainly be presented at the forthcoming ECTS-supported *6th International Conference on Children's Bone Health* (ICCBH), to be held in June 2013 in Rotterdam (Netherlands).

Conflict of Interest

The author declares no conflict of interest.

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