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Meeting Report Open Access

Glucocorticoids Action in Bone and Cartilage: A Report from 9th Joint Meeting of Pediatric Endocrinology

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Glucocorticoids (GCs) are commonly used to treat inflammatory diseases and cancers. A multitude of undesired side effects have been reported in GC-treated patients including reduced bone mineral density and decreased linear bone growth. Recent studies confirm that systemic glucocorticoid (GC) therapy is not only associated with an increased risk of bone fragility (osteoporosis) but also impairs linear bone growth in childhood. The 9th Joint Meeting of Pediatric Endocrinology was held in Milan, Italy, 2013. The meeting attracted clinicians and scientists from all parts of the world actively engaged in pediatric endocrinology to discuss their ongoing studies and exchange technical information. The program also consisted of three seminars/presentations on the use of GCs and its side effects in children, all followed by discussions. This report summarizes the data presented on GCs-induced bone growth impairment in children.

Leanne M Ward focused on clinical aspects of Glucocarticoids use and reviewed data that showed children prescribed 4 or more, one week courses of oral steroids have a four-fold increased risk of extremity fractures. Dr. Ward also discussed in depth vertebral fractures (VF), an important manifestation of osteoporosis in this setting, occurring in up to 35% of GC-treated children with serious diseases such as leukemia, rheumatic conditions and Duchenne muscular dystrophy. She further discussed that prospective surveillance studies of GC-treated children with leukemia and rheumatic conditions have shown that most of the VF burden occurs in the first 12 to 24 months of GC exposure, that VF are frequently asymptomatic, and that children with a history of VF (including mild vertebral collapse) are at increased risk for future spine fractures. On the other hand, children with transient bone health threats have the unique potential for vertebral body reshaping, either spontaneously or with bone-specific treatment. Recovery from fracture-induced deformity with reshaping of vertebral bodies is growth-dependent, underscoring the importance of timely diagnosis and intervention. Prevention begins with optimization of conservative measures, including physical activity, calcium and vitamin D intake, plus treatment of endocrinopathies and aggressive treatment of the underlying disease using the lowest effective GC dose. These measures may be insufficient to prevent fractures in some, raising the need for bone-specific therapy. Since bone-targeted treatment is typically reserved for children with overt fragility, careful monitoring to avoid advanced osteoporosis presentations is paramount. Bisphosphonates are the most commonly prescribed agents in children; however, interest in the use of novel osteo-anabolic therapy is mounting given bone Histomorphometric observations that GC-associated osteoporosis in children is typically characterized by significant reductions in bone turnover.

Faisal Ahmed discussed both basic and clinical aspects of chronic diseases such as inflammatory bowel disease and, particularly Crohn's disease (CD); CD can cause cause growth failure during childhood as well as a reduction in final adult height. The underlying mechanism is multifactorial and includes poor nutrition, chronic inflammation, and the prolonged use of steroids. It is possible that these factors work in combination to induce a state of GH resistance systematically as well as at the level of the rowth plate. Addressing these aspects should lead to an improvement in growth but despite major advances in the treatment of such conditions, a substantial cohort of children continues to display a deficit in linear growth and may qualify for growth-promoting hormonal therapy. Whilst there are some studies of growth hormone therapy in children with chronic inflammation and long-term glucocorticoid therapy, there is little evidence to support widespread and long-term use of these drugs. There is an additional concern that this may be associated with an alteration on insulin sensitivity in a group of children who are already predisposed to this abnormality. Farasat Zaman presented summary of pre-clinical studies that GCs not only inhibit proliferation and differentiation potential of chondrocytes but also trigger undesired chondrocyte apoptosis by activating caspase 8, 9 and 3, along with suppression of the Akt-PI3K signaling pathway. GCs treatment triggers Bax-mediated mitochondrial injury in proliferative chondrocytes causing growth retardation in young mice. Dr. Zaman also discussed their recent study where they used rare tissue samples of cultured human growth plate cartilage obtained from children undergoing epiphyseal surgery, which showed increased level of pro-apoptotic protein Bax and DNA fragmentation when exposed to GCs. Interestingly, anti-Bax and anti-Bid small interfering RNA rescued the chondrocytes from undesired GCs-induced apoptosis and mice lacking Bax were completely protected from GCs-induced bone growth impairment. These data suggests to also explore non-conventional targets such as inactivation of Bax by using small molecules/peptides which may provide a new potential strategy to minimize adverse effects of GCs on bone growth.

In conclusion, this session on use of GCs-induced bone growth impairment in children in 9th joint meeting of pediatric endocrinology gave a succinct update and highlighted the need of further investigations on how to prevent side effects of GCs on bone tissue through new treatment strategies.

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