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EDITORIAL

Could zinc supplementation improve bone status in growth hormone (GH) deficient children?

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Editorial

Reduced bone mineral density (BMD) and increased fracture rate have been reported in subjects with either childhood or adult onset growth hormone (GH) deficiency (GHD), more severe in childhood onset GHD [1, 2]. A longer gap in GH replacement in adults with childhood onset GHD is associated with a lower bone mineralization and GH replacement has been suggested having a critical role in transition to adulthood to optimize bone accrual [3]. Furthermore, also a delay in starting GH replacement in GHD adults may be associated with a persistent increase in vertebral fracture risk [4]. However, many criticisms have been raised on these assumptions. Limitations of current bone imaging techniques have caused many artefacts about BMD and bone structure. Using appropriate size corrections, BMD is normal in children and adults with isolated GHD in several studies and the anabolic changes in muscle mass and strength may contribute to the observed bone changes [for critical reviews see 5, 6]. Briefly, many historical studies used T-scores in GHD children, comparing children's BMD with adult reference data. On the other hand, when age—and sex—Z scores have been introduced for the pediatric population, height remained a confounding factor and being tall or short for age leads to a false negative or a false positive result for BMD Z-score, respectively. Since 2008, official positions of the International Society for Clinical Densitometry strongly recommend size correction for DXA measurements in the pediatric age [7]; however, no consensus exists how to correct measurements. To date, the most real effect of GHD on bone seems to be a reduction in bone volume ratio and trabecular thickness in both animal and human studies [5, 6]. Moreover, we must not forget that GH replacement causes biphasic effects on the bone remodeling with early stimulation of bone resorption followed by a sustained increase in bone formation [8]: some controversial results of published literature could be due to the time from the start of the therapy. On the other hand, it is unclear whether changes in BMD may really predict the fracture risk in patients with GHD, as well as other forms of secondary osteoporosis, being other markers of bone quality still searched.

The first point in favor of the paper by Ekbote et al. [9] in this issue of *Endocrine* is that the Authors performed size correction for DXA bone mineral content (BMC) and bone area (BA) measurements using height. They showed that in Indian prepubertal children with isolated GHD, height adjusted BMC and BA significantly increased of 48 and 40 %, respectively, after 1 year of GH treatment. These changes were associated with an increase in height adjusted lean body mass and a decrease in height adjusted body fat. Many previous studies in childhood onset GHD, in particular in Italian and Dutch cohorts, reported an increase in BMC in the range of 2–10 %, significantly lower than that observed in the present study [5, 6]. However, it has to be emphasized that the majority of other studies did not perform any size correction. Furthermore, the population investigated in this study [9] presented a very low BMC at baseline and this aspect could have influenced the results. However, we can first speculate that when BMC is clearly reduced in GHD patients, a treatment with rhGH works in improving bone health.

Bone metabolism is complex. Many factors tightly regulate BMC and bone accrual, mainly, among others,

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vitamin D and calcium. Moreover, GH also with IGF-I modulates vitamin D, PTH, calcium and phosphate metabolism by acting in a multifaceted interplay [6]. Thus, the second point well underlined by the paper by Ekbote et al. [9] is that the Authors have considered bone metabolism in GHD as a network and they have evaluated whether vitamin D, calcium, and zinc supplementation can improve together bone mineralization together with GH treatment. They stated that poor dietary intakes of zinc and calcium associated with vitamin D deficiency, a condition common in many countries, could all contribute to an impairment of bone mineralization in GHD. On the other words, they assumed that because the system is complex the best results are reached when the intervention is more complete. In the second year of the study they treated a group (group A) with calcium (500 mg/daily), vitamin D (cholecalciferol, 60,000 UI every 3 months), and GH and another one (group B) with calcium, vitamin D, zinc (Zynconia Syrup), and GH. Interestingly, in the second year group B presented a higher growth velocity and higher IGF-I levels with respect to group A. They also showed a greater height adjusted percentage gain in BMC, BA, and lean body mass. It has to be underlined that despite supplementations, the calcium and zinc intakes were still in the order of 65 % of RDA for each group. A recent meta-analysis have suggested that vitamin D supplementation in children and adolescents who are deficient can bring them to improvements in lumbar spine BMD and total BMD [10]. Similar results were demonstrated in an Italian prepubertal cohort [5]. Moreover, zinc supplementation improved growth velocity in at least two studies in GHD children [11, 12]. If the role of vitamin D and calcium in bone homeostasis is well known, the role of zinc is often forgotten or widely unknown. Zinc is able to enhance the action of vitamin D in bone formation, and also the GH effects on bone [12]. Zinc concentrations in bone are very high being considered an essential component of the calcified matrix. It also has a stimulatory effect on osteoblastic bone formation through collagen synthesis and an inhibitory effect on osteoclastic bone resorption. Zinc enhances the anabolic IGF-I effects in osteoblastic cells by exerting a complex network. Although the pediatric population treated in this study presented a suboptimal dietary intake which cannot mirror other populations and it is also relative small, the results suggest that many factors can be involved in the impairment of bone quality and accrual in childhood onset GHD. A more holistic approach to complex systems could help to reach goals in clinical practice. Focusing on bone in GHD, a longitudinal adequately powered trial is needed to understand whether substitution of other nutrient deficits crucial for bone metabolism together with GH therapy could really improve BMC, BMD, or, as previously discussed, other markers of bone quality in secondary osteoporosis. To date, a punctual dietary assessment in GHD children is mandatory to improve our intervention and it should be food for thought.

Conflict of interest The authors declare they have no conflict of interest.

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