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Effect of growth hormone therapy and puberty on bone and body composition in children with idiopathic short stature and growth hormone deficiency

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Abstract

The state of bone health and the effect of growth hormone (GH) therapy on bone and body composition in children with idiopathic short stature (ISS) are largely unknown. A direct role of GH deficiency (GHD) on bone density is controversial. Using dual-energy X-ray absorptiometry, this study measured total body bone mineral content (TB BMC), body composition, and volumetric bone mineral density (vBMD) at the lumbar spine (LS) and femoral neck (FN) in 77 children (aged 3–17 years) with ISS ($n = 57$) and GHD ($n = 20$). Fifty-five children (GHD = 13) receiving GH were followed over 24 months including measurement of bone turnover. At diagnosis, size-corrected TB BMC SDS was greater ($P \leq 0.002$) and LSvBMD SDS lower ($P < 0.03$) than zero in both prepubertal ISS and GHD subjects, but FNvBMD SDS was reduced only in the GHD group ($P < 0.05$). The muscle-bone relation, as assessed by the BMC/lean mass (LTM) ratio SDS was not different between groups. During GH therapy, prepubertal GHD children gained more height (1.58 [0.9] SDS) and LTM (0.87 [0.63] SDS) compared to prepubertal ISS children (0.75 [0.27] and 0.17 [0.25] SDS, respectively). Percent body fat decreased in GHD (−5.94% [4.29]) but not in ISS children. Total body BMC accrual was less than predicted in all groups accompanied by an increase in bone turnover. Puberty led to the greatest absolute, but not relative, increments in weight, LTM, BMI, bone mass, and LSvBMD. Our results show that children with ISS and GHD differ in their response to GH therapy in anthropometry, body composition, and bone measures. Despite low vBMD values at diagnosis in both prepubertal groups, size-corrected regional or TB bone data were generally within the normal range and did not increase during GH therapy in GHD or ISS children. Growth hormone had great effects on the growth plate and body composition with subsequent gains in height, LTM, bone turnover, and bone mass accrual, but no benefit for volumetric bone density over 2 years.

Keywords: Idiopathic short stature; Growth hormone deficiency; Osteopenia; Bone density; Children; Body composition

Introduction

Idiopathic short stature (ISS) represents a heterogeneous group of short children in whom the cause of decreased childhood growth cannot be identified. Treatment with growth hormone (GH) in ISS results in a small but significant gain in final height [1–3]. Apart from one longitudinal study which reported low areal bone mineral density (BMD) at the lumbar spine in a small ISS cohort which normalized during GH therapy [4], no studies have so far addressed bone health and body composition in ISS children.

In contrast, numerous studies have assessed the effect of GH on bone density and body composition in children and adults with GH deficiency (GHD). Both GH and IGF-

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I have a well-recognized role in bone elongation and skeletal maturation in vitro and in vivo [5–8]. However, a direct role of GH for mineral accrual and bone density is controversial. Adults with severe, untreated isolated childhood-onset GHD [9,10] or complete GH insensitivity [11,12], as well as children with partial GH insensitivity [13] have been reported with normal size-corrected BMD and no increased number of fractures [10,14]. In addition, bone health is mainly assessed by dual-energy X-ray absorptiometry (DXA), a two-dimensional technique prone to size-dependent artifacts in children, particularly with short stature. Adjustments for bone or body size are thus essential in the interpretation of DXA data [15–17]. The increase in bone mineral content (BMC) or areal BMD *z* scores observed during GH treatment [18] is mostly caused by the GH-induced gain in height, but also in muscle strength and mass [19] which independently increases bone strength [20]. Lean mass [21,22], muscle size [23], and, to a lesser degree, estimated volumetric BMD (g/cm^3) are low at diagnosis of GHD [21,22,24] but increase during GH therapy [13,21, 22,25]. A decreased accrual in bone mass [26,27] and lean mass [28–30] is seen at withdrawal of GH therapy during transition from adolescence to young adulthood, which can be reversed by retreatment with GH [27,31], suggesting a positive role of GH on bone health.

Some previous studies are biased by inappropriate size-correction for DXA variables but also by not accommodating for the effect of puberty on bone mass, which may result in erroneous interpretation of DXA data if groups are inappropriately matched for pubertal stage. The present longitudinal study compares cohorts of children and adolescents with ISS and GHD with the main purposes (1) to differentiate the effects of GH therapy and puberty on bone and muscle mass, body composition, anthropometry, and bone turnover, and (2) to examine total body and regional bone scans by applying size-corrections to the areal DXA output with special consideration to the muscle–bone relation at the total body.

Subjects and methods

The study cohort comprised 77 patients (mean [SD] age 10.90 [3.12] years, 25 girls) with short stature, seen by endocrinologists at The Children's Hospital at Westmead, Sydney, Australia. The assessment of short stature involved at least one GH stimulation test. Subjects were classified as having GHD if peak GH was <10 ng/ml following 2 stimulation tests and ISS if peak GH response to stimulation was >10 ng/ml. Other causes of short stature were excluded by clinical and biochemical examination. Six individuals of the GHD group were treated with thyroxine for TSH deficiency and remained euthyroid throughout the study. Three individuals in the GHD group received Hydrocortisone replacement in a dose of 6–8 mg/m^2/day. All patients had a growth velocity <25th centile for age and fulfilled the Australian criteria for GH treatment. Bone densitometry, anthropometry, bone age, pubertal stages, and bone markers were assessed before the commencement of GH (baseline) and after 6, 12, and 24 months. The mean (SD) GH dose at onset was 5.23 (2.74) mg/m^2/week [0.026 (0.007) mg/kg/day]. This lower dose, in comparison to the higher doses currently recommended, was used as this longitudinal study was performed in the 1990s. The patients were seen at 3 monthly intervals for clinical assessment. Adjustment of GH dose occurred every 6 months to maintain catch-up growth. The GH dose increased significantly during the study period to 6.37 (2.78) mg/m^2/week [0.027 (0.008) mg/kg/day]. The increase was not different between groups.

At commencement of GH therapy, 52 subjects (GHD, $n = 20$) were prepubertal and 25 pubertal (all ISS). Twenty patients (GHD, $n = 5$) dropped out of the study or did not attend the 2-year visit. Their 1st year growth velocity, baseline anthropometric *z* scores, and growth hormone dose were not different from the longitudinal study population. At the 2-year visit, two of the prepubertal GHD group and 13 of the prepubertal ISS group had entered puberty. The pubertal GHD group ($n = 2$) was excluded from longitudinal analysis. Therefore, complete longitudinal 2-year data sets were available for 55 patients (16 girls). These patients were then categorized into "remaining prepubertal" (ISS = 13, GHD = 13) and "pubertal", meaning having gone into puberty or remaining pubertal ($n = 29$, all ISS). The Institutional Ethics Committee approved the study and informed consent was obtained from all subjects and families.

Methods

Anthropometry

Height was measured with a Harpenden stadiometer to the nearest 1 mm and weight with an electronic scale to the nearest 20 g on the day of the DXA scan. Height and weight *z* scores (SD scores) were calculated according to sex and age [32]. For subjects over 18 years, height and weight *z* scores were calculated as for an 18-year-old. Sex-specific body mass index (BMI in kg/m^2) *z* scores for age were calculated from data derived from Cronk and Roche [33]. Pubertal stages were assessed according to Tanner [34].

Densitometry

A pencil beam DPX (Lunar Corp, Madison, WI) total body scanner with adult software (version 3.4) was used to perform DXA measurements on all subjects. Analysis was done with software version 4.7 by a single technician. The technique and measurement protocol, including quality-assurance testing, has been described previously [35,36]. In brief, the coefficients of variation for total body (TB) BMC, lean tissue mass (LTM), and percent fat mass were 0.74, 0.82, and 1.59%, respectively. Total body measurements were compared to our normative data set of healthy females