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Deficits in Bone Geometry in Growth Hormone-Deficient Prepubertal Boys Revealed by High-Resolution Peripheral Quantitative Computed Tomography

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Growth hormone deficiency · Bone · HR-pQCT · Pediatric endocrinology

Abstract
Introduction: Although growth hormone (GH) is essential for attainment of peak bone mass, bone health in prepubertal children with GH deficiency is not routinely evaluated. The objective of this study was to evaluate bone microarchitecture in GH-deficient (GHD) boys using high-resolution peripheral quantitative computed tomography (HR-pQCT). ***Methods:*** Fifteen control and fifteen GHD, GH naïve pre-pubertal boys were recruited for a case-control study at a major academic center. Subjects with panhypopituitarism, chromosomal pathology, chronic steroids, or stimulant use were excluded. Volumetric bone mineral density (vBMD; total, cortical, and trabecular), bone geometry (total, cortical and trabecular cross-sectional area, cortical perimeter), bone microarchitecture, and estimated bone strength of the distal radius and tibia were assessed by HR-pQCT. Areal BMD and body composition were assessed by DXA. Insulin-like growth factor 1 (IGF-1), osteocalcin, C telopeptide, and P1NP levels were measured. ***Results:*** GHD subjects had a significantly smaller cortical perimeter of the distal radius compared to controls ($p < 0.001$), with the difference in cortical perimeter persisting after adjusting for height *z* score, age, lean mass, and 25-hydroxyvitamin D level ($p < 0.05$). No significant differences were found in vBMD. No significant differences were found in microarchitecture, estimated strength, areal BMD, body composition, or bone turnover markers. Analysis showed significant positive correlations between IGF-1 levels and cortical parameters. ***Discussion/Conclusions:*** Prepubertal GHD boys had deficits in bone geometry not evident with DXA. Larger prospective/longitudinal HR-pQCT studies are needed to determine the extent of these deficits, the need for routine bone evaluation, and the timing of GH replacement for prevention or restoration of these deficits.

Introduction

Although growth hormone (GH) is responsible for longitudinal bone growth, it also plays an important role in building and maintaining bone mineral density (BMD)

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and in altering bone architecture throughout life [1, 2]. GH, by acting directly and by stimulating insulin-like growth factor 1 (IGF-1), is essential for achieving peak bone mass, and contributes to mitigating the risk of osteoporosis and subsequent fracture in the future [2–5]. GH deficiency during childhood and puberty may compromise accrual of bone mass and formation of normal bone architecture because a significant amount of bone mass is achieved by the end of puberty, with peak bone mass achieved during the late second to early third decade of life [3, 6]. Even though GH-deficient (GHD) prepubertal children may not be at risk for fractures, studies have shown that untreated children with GH deficiency (mean age 7–11.7 years) have lower dual X ray absorptiometry (DXA) measures of bone mineral apparent density (BMAD, as an estimate of volumetric BMD) of the lumbar spine, radius, and total body [2, 7–9], while untreated adults with GH deficiency have increased fracture risk as well as lower BMD scores [10–12].

Prior studies in GHD children have evaluated BMD using DXA, though this method has significant disadvantages. Measurements are affected by size, thereby underestimating BMD in people with smaller stature [13]. Additionally, DXA only measures areal BMD from a 2-D projection of bone and does not measure actual vBMD (volumetric BMD). Resolution of the images is low, and DXA cannot be used to assess BMD in the cortical and trabecular bone separately or assess microarchitectural characteristics that also contribute to bone strength [14–16].

High-resolution peripheral quantitative computed tomography (HR-pQCT) is a state-of-the art imaging technology that can scan human subjects in vivo at resolutions high enough to enable characterization and evaluation of volumetric density, geometry, and microarchitecture. As the resolution is high (voxel size 61 μm), it even allows for segmentation of trabecular and cortical bone and their respective evaluation. Bone microarchitecture and bone density contribute to increased bone strength [17, 18] which can decrease risk of fracture in children [19, 20]. Knowledge regarding the effects of GH deficiency on skeletal health is limited though because bone parameters are not routinely evaluated in young children with GH deficiency. A recent HR-pQCT study in adults with childhood-onset GH deficiency who were no longer receiving GH replacement showed deficits in vBMD, architecture, and bone strength [21]. Schweizer et al. [22] performed the only study evaluating trabecular and cortical bone compartments in the pediatric GHD population, using a lower-resolution imaging technique (peripheral QCT) with the inability to evaluate microarchitectural bone features. Additionally, studies using HR-pQCT in healthy children tend to focus on the adolescent or peripubertal populations [23, 24]. Proper characterization of bone health in young, prepubertal GHD children has significant implications for a critical window of intervention which can impact long-term bone health.

The primary goal of this study was to use HR-pQCT to evaluate bone geometry, vBMD, bone architecture, and bone strength in GHD pre-pubertal boys compared to healthy control subjects. The relationship between GH levels, IGF-1 levels, bone markers, and HR-pQCT measures was also assessed in the GHD cohort.

Materials and Methods

Participants

A total of 30 boys, 5–11 years of age were recruited between 2016 and 2018 from the general pediatric practices and the pediatric endocrinology practice associated with Columbia University Medical Center, as well as other nearby practices. Informed consent was obtained from a parent or legal guardian, and assent was obtained for children >7 years of age. The study was approved by the Institutional Review Board of Columbia University Medical Center. All participants were assessed as prepubertal based on evaluation of testicular size <4 cm^3 and had no disabilities that would limit normal physical activity. Fifteen boys had isolated GHD and were naive to therapy. Along with height and growth velocity measurements, the diagnosis of GHD was reconfirmed with a peak serum GH level <10 ng/mL in response to 2 stimulation tests (clonidine/arginine, glucagon, or arginine/L-dopa) [25]. All bone age (BA) studies were documented and assessed by the pediatric endocrinologist and the radiologist. Standards of Greulich and Pyle were used to estimate BA. Fifteen subjects with heights between the 3rd and 97th percentiles who were healthy, with no concerns regarding height or growth velocity served as controls and were recruited from the general pediatric practices affiliated with Columbia as well as other nearby practices. Control and GHD subjects were not matched for height, as that would have required including much younger control subjects. Neither control nor GHD participants had chronic health issues (beyond GHD) that would interfere with bone health, and all were ambulatory. Children with panhypopituitarism, chromosomal diagnosis, or on chronic medication, including levothyroxine, systemic or inhaled steroids, or stimulants, were not included. Use of intermittent antihistamines and vitamin supplementation was allowed. All children were born at appropriate size for gestational age. Nutritional history was not formally evaluated. Ethnicity was determined based on parental self-report. In the control group, there were 9 Hispanic children, 4 Caucasian children, 1 African-American child, and 1 Asian child. In the GHD group, there were 7 Hispanic children, 4 Caucasian children, 1 African child, 2 Asian children, and 1 Middle Eastern child.

Anthropometric Data Acquisition

Standing heights and weights were measured using a wall-mounted stadiometer and electronic scale, with participants dressed in light clothing. To determine growth velocity from med-

Table 1. Subjects' characteristics

	Control (n = 15)	GHD (n = 15)	p value
Demographics			
Height Z score	–0.39±1.0	–2.27±0.61	<0.001*
Tibial length, mm	271.67±27.88	249.33±21.20	<0.001*
Radius length, mm	183.28±22.09	173.8±16.48	0.469
Age, years	7.82±1.32	8.85±1.21	0.035*
Hispanic ethnicity (%)	9 (60)	7 (47)	0.714
BMI %ile	57.27±27.3	38.61±28.21	0.097
25-hydroxyvitamin D, ng/mL	25.62±6.39	22.4±8.36	0.251
IGF-1, ng/mL	n/a	140.93±66.57	n/a
Peak growth hormone level, ng/mL	n/a	5.62±2.25	n/a
Bone turnover markers			
CTX, ng/mL	1.63±0.42	1.72±0.52	0.702
OC, ng/mL	116.61±51.59	98.81±46.36	0.338
PINP, μg/mL	572.87±146.39	489.99±162.36	0.160
DXA			
Whole body (subtotal) BMD, g/cm^2	0.61±0.06	0.57±0.06	0.088
Whole body BMD Z score	0.14±0.75	–0.29±0.65	0.109
AP spine BMD, g/cm^2	0.54±0.07	0.51±0.06	0.255
AP spine BMD Z score	0.15±1.06	0.15±0.84	0.999
1/3 forearm BMD, g/cm^2	0.48±0.05	0.46±0.43	0.229
1/3 forearm BMD Z score	0.36±1.37	0.11±0.81	0.547
R arm area, cm^2	102.07±12.59	95.69±11.70	0.180
Fat mass, g	6,718.73±2,738.89	5,919.33±2,133.86	0.290
Lean mass, g	17,827.72±3,306.08	15,778.33±2,992.67	0.086
Percent fat	25.71±5.73	26.17±6.38	0.839
Visceral adipose tissue, g	151.33±67.13	146.73±44.29	0.827

Summary statistics for demographics, bone turnover markers, and DXA. Values shown as mean ± SD or n (%); p values generated by two-sample t test or χ^2 test; * p value <0.05.

ical records in GHD subjects, height measurements were taken at intervals of 4–6 months. Radial length was assessed as the distance from the olecranon to the ulnar styloid process, measured medially with elbow flexed at a 90-degree angle and palm facing inward. Tibial length was assessed as the distance from the medial malleolus to medial tibial plateau, measured with the knee flexed at a 90-degree angle to the floor [24].

Calculated vBMD and Body Composition Acquisition Using DXA

DXA scans were obtained at the Body Composition Unit of Columbia University Medical Center. DXA scans of the whole body excluding head, posteroanterior lumbar spine (L1–L4) and right forearm were obtained using Hologic QDR 4500 in array mode (Hologic Inc., Waltham, MA, USA). Scans were analyzed using APEX 4.5.3 software and read by 2 certified densitometrists in the division of pediatric endocrinology (A.S. and I.F.) for quality assurance. Height correction was performed for all subjects [26].

Bone Architecture, vBMD and Strength Acquisition with HR-pQCT

Trabecular and cortical vBMD and microarchitecture were assessed using HR-pQCT (XtremeCT-II, Scanco Medical, Brüttisellen, Switzerland). Each subject's right radius and tibia were scanned and placed in a carbon-fiber cast to minimize limb motion during scan acquisition. If the subject had a history of fracture in the right limb, then the left limb was scanned. A standard anteroposterior scout view was taken (fixed settings of the machine) to assess the growth plate and then place the reference line at the most proximal end of the growth plate in order to ensure that the growth plate was not irradiated, although the radiation dosage was very minimal (<5 μSv/scan). A 10.2-mm scan region comprising of 168 slices with an isotropic voxel size of 61 μm was acquired at both sites. The scans were acquired at a relative offset to the most proximal slice from the reference line; the offset being 4.5 and 7% of the limb length at radius and tibia, respectively. Due to possible differences in height and limb length in these growing children, it was crucial to use a relative offset in order to scan the same or similar regions of interest across the cohort. This relative offset ensured that the same scan region was obtained despite varying limb lengths. Scans were performed using the standard manufacturer in vivo imaging protocol [27, 28]. All scans were assessed for motion on a scale of 1–5 with 1 indicating no motion and 5 indicating significant motion [29], and scans with motion scores >3 were excluded from the analysis (1 radius, 1 tibia). Scans were obtained and analyzed by a single qualified technician in order to minimize interoperator variability.

Finite element analysis (FEA) was performed using the HR-pQCT images to estimate whole bone stiffness (N/mm) and failure load (N) [30, 31]. Uniaxial compression was simulated to 1% strain using a homogeneous Young's modulus of 6,829 MPa and Poisson's ratio of 0.3 [32] to estimate stiffness. Failure load (FL) was estimated based on the criterion by Pistoia et al. [33]. We used a commercial FE solver (FAIM, v7.1; Numerics88, Calgary, AB, Canada) on a desktop workstation (Linux CentOS 7.1, 2 × 6-core Intel Xenon, 64 GB RAM) to solve the models.

The CV (%) (coefficient of variation) for DXA sites at our center is LS (lumbar spine) <1% FN (femoral neck) <1.5%, forearm <1%, body composition 1%. For HR-pQCT (XtremeCT II) at our center, all density measures are <1% at both distal radius and tibia, microarchitecture <4.5% at both sites with the exception of Ct.Po being <16% at radius and <10% at tibia, FEA measures (stiffness and FL) <7% at radius and <3% at tibia.

Biochemical Assays

Fasting blood samples were obtained and stored for batch analysis. Serum osteocalcin and C telopeptide were measured by ELISA, and PINP measured by radioimmunoassay, all from Immunodiagnostic Systems (Gaithersburg MD). Growth hormone and IGF-1 assays were run by IDS-iSYS Specialty Immunoassay System at the Pathology's Clinical Pharmacology and Toxicology Laboratory at the Irving Institute for Clinical and Translational Research, Columbia University Medical Center (New York, NY, USA). 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 were measured using ultra-performance liquid chromatography-tandem mass spectrometry by the Biomarkers Core Lab, Irving research Institute for Clinical and Translational Research, Columbia University Medical Center (New York, NY, USA).

Statistical Methods

Descriptive statistics were used to summarize participants' characteristics by group: GHD and control subjects. Continuous measurements were expressed as mean ± standard deviation or median (interquartile range), and differences between the two groups were tested using two-sampled *t* tests or Wilcoxon rank-sum tests for measurements non-normally distributed. Linear regression models were employed to assess differences in HR-pQCT measurements between GHD and control subjects, adjusting for age, height standard deviation score, lean mass, and 25-hydroxyvitamin D level. Spearman correlation coefficients were used to quantify the strength of association between HR-pQCT parameters and bone turnover markers, GH, and IGF-1 levels, respectively. All statistical tests were two tailed, and *p* values <0.05 were considered statistically significant.

Results

Clinical, Anthropometric, and Biochemical Characteristics

Clinical, anthropometric and biochemical parameters characterizing our cohort are presented in Table 1. GHD prepubertal males were on average 1 year older, and as expected significantly shorter than controls (height *z* score in GHD group –2.27 ± 0.61 vs. controls –0.39 ± 1; $p < 0.001$). Although GHD subjects were shorter, there was no significant difference in limb length of the radius between the two groups ($p = 0.47$). Height differences were due to differences in tibial length ($p < 0.001$) and likely differences in trunk length (though not measured in this study). No significant difference in the BMI percentile was found among the groups, with actual BMI ranging between 14.0 and 19.6 kg/m^2 across all participants. GHD prepubertal males had IGF-1 *z* score of –0.23 ± 1.26 and a BA of 7.2 ± 1.8 (–2.1 standard deviations below the mean for chronological age) with an annual growth velocity of 4.2 ± 0.55 cm/year (<10th percentile for age). All subjects were vitamin D sufficient. There were no significant differences between GHD and control groups in absolute values of bone formation and resorption markers.

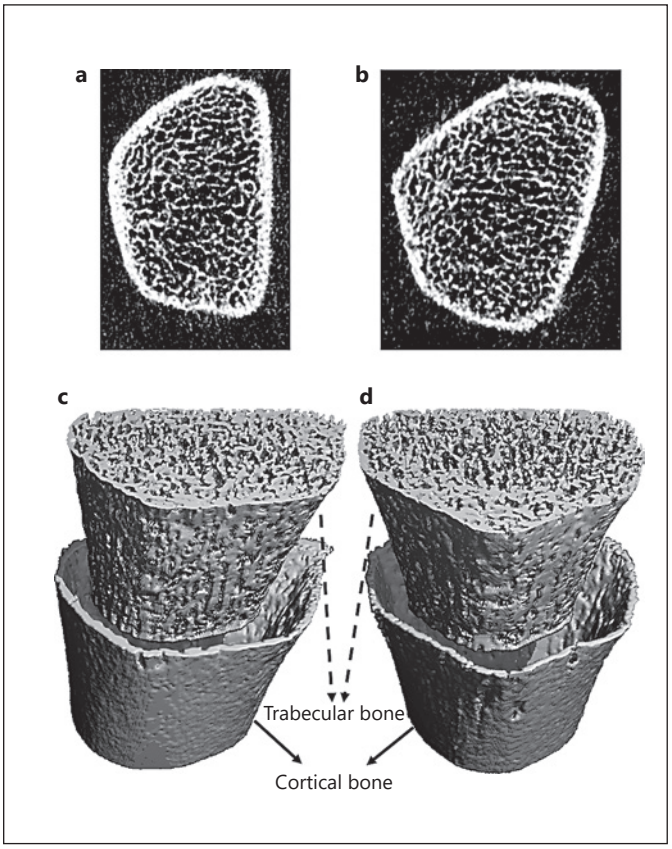

Fig. 1. HRpQCT scan of distal radius in growth hormone-deficient (left) and control (right) subjects. **a**, **b** A single cross-sectional slice of the scan showing the geometry and microstructure of the bone. **c**, **d** The segmented trabecular and cortical bones.

DXA

No significant differences between the GHD and control groups were found in bone-projected area at the ra-

Table 2. Summary statistics for HR-PQCT radius.

	Control (n = 15)	GHD (n = 15)	p value
HR-pQCT radius			
Total cross-sectional area, mm^2	139.18±23.78	109.57±17.89	<0.001*
Cortical perimeter, mm	46.76±3.71	41.18±3.59	<0.001*
Cortical cross-sectional area, mm^2	30.24±5.84	27.04±4.99	0.123
Trabecular cross-sectional area, mm^2	111.41±24.15	84.74±15.05	<0.001*
Total vBMD, mg HA/cm^3	289.67±50.73	297.17±28.5	0.632
Trabecular VBMD, mg HA/cm^3	179.3±42.59	164.02±26.51	0.513
Cortical vBMD, mg HA/cm^3	695.74±65.41	731.25±26.96	0.076
Trabecular number, 1/mm	1.79±0.26	1.66±0.16	0.110
Trabecular thickness, mm	0.21±0.02	0.21±0.01	0.271
Cortical thickness, mm	0.74±0.16	0.75±0.11	0.721
Cortical porosity	0.01±0.001	0.01±0.001	0.947
Stiffness, N/mm	16,578.79±5,489.55	14,835.87±3,677.58	0.321
Failure load, N	881.79±283.96	778.07±200.75	0.263
HR-pQCT tibia			
Total cross sectional area, mm^2	524.18±66.20	478.99±81.71	0.124
Cortical perimeter, mm	89.29±6.32	85.33±7.90	0.159
Cortical cross-sectional area, mm^2	60.48±14.41	51.59±10.16	0.088
Trabecular cross-sectional area, mm^2	468.30±65.22	431.79±74.92	0.184
Total vBMD, mg HA/cm^3	259.22±36.01	252.83±29.46	0.609
Trabecular VBMD, mg HA/cm^3	206.06±31.48	203.53±29.65	0.475
Cortical vBMD, mg HA/cm^3	684.12±33.58	682.07±31.07	0.868
Trabecular number, 1/mm	1.84±0.19	1.81±0.17	0.696
Trabecular thickness, mm	0.24±0.02	0.24±0.02	0.984
Cortical thickness, mm	0.76±0.21	0.67±0.14	0.128
Cortical porosity	0.01±0.01	0.01±0.01	0.580
Stiffness, N/mm	59,011.38±20,135.76	54,980.93±21,664.78	0.616
Failure load, N	3,032.08±935.43	2,625.93±858.27	0.242

Values shown as mean ± SD; p values generated by two-sample t test test; * p value <0.05.

dius ("R arm area"), whole body minus head, 1/3 forearm or AP spine volumetric BMD or BMD z score. Fat mass, lean mass, percent fat, and visceral adipose tissue did not differ significantly between the two groups (Table 1). Interestingly in GHD subjects, IGF-1 levels had a positive correlation with whole-body areal BMD (r = 0.73, p = 0.003) as well as lean mass (r = 0.76, p = 0.002). As expected in GHD subjects, peak stimulated growth hormone levels had a negative correlation with percent fat (r = –0.64, p = 0.01) and visceral adipose tissue (r = –0.66, p = 0.01).

HR-pQCT Measurements at the Distal Radius and Tibia

Bone Geometry and Structure

At the radius, GHD subjects had significantly smaller cortical perimeter indicating narrower bones, when compared to controls (Fig. 1). Trabecular cross-sectional area was on average 24% smaller, and cortical perimeter was on average 12% smaller in GHD subjects compared to controls (p < 0.001) (Table 2). The difference in cortical perimeter persisted after controlling for height z score, age, lean mass, and 25-hydroxyvitamin D level. Regression analysis showed that on average, GHD prepubertal males had 4.20 mm smaller cortical perimeter (p < 0.05) compared to controls (Table 3). In the GHD group, IGF-1 correlated significantly with cortical parameters (cortical vBMD, cortical cross-sectional area, and cortical thickness) at the radius with coefficients ranging from r = 0.60 to 0.80 (all p < 0.05). None of the geometric parameters were significantly different between the groups at the tibia.

Volumetric BMD, Microarchitecture, and Estimated Bone Strength

No significant differences between the two groups were found in total, cortical, or trabecular vBMD or any of the microstructure parameters in both the radius and

Table 3. Regression analysis results for two different outcomes, controlling for height *Z* score, age, lean mass, and 25-hydroxyvitamin D level

	Estimate	Std. error	*p* value
Outcome: cortical perimeter			
Intercept	38.79	4.99	<0.0001
GHD (vs. control)	–4.21	1.96	0.043
Height *Z* score	1.85	1.06	0.094
Age	1.70	0.99	0.100
Lean mass	–0.0001	0.001	0.724
Vitamin D	–0.07	0.08	0.378
Outcome: trabecular cross-sectional area			
Intercept	47.21	27.72	0.103
GHD (vs. control)	–17.99	10.87	0.112
Height *Z* score	7.98	5.87	0.188
Age	8.16	5.50	0.152
Lean mass	–0.0001	0.002	0.953
Vitamin D	0.192	0.449	0.673

tibia. Stiffness and failure load as measures of estimated bone strength did not differ significantly between the two groups (Table 2).

Discussion/Conclusions

This study evaluated prepubertal GHD young boys using HR-pQCT. The results of our study provide novel insights into the structural characteristics of cortical and trabecular bone architecture in prepubertal boys diagnosed with GHD using a state-of-the-art technology. Standard bone morphology in the skeleton and as observed at the radius and tibia from HR-pQCT scans is comprised of trabecular bone surrounded by cortical bone with a surrounding periosteum. Our study demonstrates that GHD prepubertal boys had bones that were narrower compared to controls after adjusting for age, height *z* score, lean mass, and 25-hydroxyvitamin D level. This was determined by a significantly smaller cortical perimeter, indicative of a smaller periosteal boundary. Studies have shown that differences in bone size between boys and girls likely contribute to differences in fracture risk later in life [34, 35], indicating the important role that bone size plays. Animal models with GHD have also demonstrated that GHD results in deterioration of bone size, microarchitecture, and mechanical properties [36].

In order to eliminate the effect of variation of limb length and ensure comparable regions when scanning, a relative offset from the reference line was used. This is important as bone geometry and microarchitecture vary along the length of long bones, with the distal (epiphysis and metaphysis) region having a dense mesh of trabecular network surrounded by a thin cortical shell. Moving proximally (towards the diaphysis), the trabecular mesh dissipates giving rise to the marrow cavity surrounded by a thick cortical shell. Hence, there is a gradient in bone properties depending on the scan region. Had a fixed offset been used, the differences in scan region would have potentially caused differences in density, geometry, and microstructure measurements across subjects, thereby confounding the actual variation between the GHD and control groups. Additionally, although limb length naturally varied between subjects, a difference in length does not imply a difference in cross-sectional area. Bones can be longer or shorter (axial length of the bone) and narrower or wider (cross section of the bone) with or without interdependence [37]. GHD prepubertal boys had a deficit in the cortical perimeter, not a deficit in length. These differences in geometry were seen only in the radius, possibly suggesting an increased tibial sensitivity to weight-bearing effects (i.e., mechanical loading due to locomotion) when compared with the radius [38], or an increased sensitivity of GHD bones to weight bearing compared to controls. Absence of differences may also be related to a lack of statistical power or some other unknown factor.

The differences in bone geometry that were seen in our cohort were not related to differences in lean or fat mass, as GHD subjects had similar body composition from DXA when compared to controls. No significant differences in vBMD, microarchitecture, bone strength, DXA measurements, body composition, or bone turnover markers were seen among the groups.

Animal models of GHD have shown deficits in bone geometry and size, and specifically in trabecular microarchitecture [36, 39–41]. Early treatment with GH in these mice was shown to fully restore trabecular microarchitecture [39] compared to other parameters that may only be restored partially. Our study did not find differences in trabecular microarchitecture, possibly because these differences might become more apparent later in puberty [42].

In contrast to our study, some prior studies using DXA in children have shown deficits in BMD in this population [2, 7–9]. However other studies have shown that when appropriate size corrections for body size were made, GHD was not associated with a significant decrease in BMD [43–47]. As DXA findings are influenced by bone size and DXA underestimates BMD when evaluating smaller bones, using HR-pQCT measurements allows for a more accurate assessment of true vBMD in these chil-

dren. Unfortunately, there are limited studies evaluating BMD using HR-pQCT in children this young, and therefore, a true reference range is not available.

No differences in body composition among the two groups were seen, though this is not surprising as alterations in body composition may only be seen in subjects with severe growth hormone deficiency [48]. We did however see associations between body composition, growth hormone, and IGF-1 levels. We found that in GHD subjects, lower peak GH levels were associated with increased fat mass, a finding supported by multiple studies showing that treatment with GH leads to a reduction in fat mass [7, 12, 49, 50]. We also found that IGF-1 was positively correlated with lean mass. Similar correlations between IGF-1 levels and lean body mass have been shown in pubertal girls [51] and children with cystic fibrosis [52]. Interestingly, IGF-1 levels in GHD subjects were also positively associated with cortical vBMD and cortical cross-sectional area, as well as whole-body areal BMD from DXA, similar to findings by Yang et al. [21] which showed that IGF-1 was positively correlated with total vBMD, cortical vBMD, and cortical area. These findings support the role of IGF-1 in muscle mass formation [53], bone health [54], and its role in the acquisition of peak bone mass [55].

The results of this study should be interpreted in the light of some limitations. It is a small, observational study and is meant to be used to generate further hypotheses in the field. It is cross-sectional, thus, associations do not prove causation. The diagnosis of GHD in childhood is challenging. We based the diagnosis of GHD on auxology, radiographic and biochemical data, and clinical judgment, which remain the foundation for the diagnosis. Our GHD subjects had a median GH level of 5.62 ng/mL, IGF-1 level of 140.93 ng/mL (123–275 ng/mL), delayed BA, and poor growth velocity. Thus, it is possible that had we limited our study to extreme cases of GHD, larger differences between the groups may have been seen. Interestingly, it has been shown that children with IGF-1 SDS < -2 did not differ significantly in anthropometric and body composition parameters from those with IGF-1 SDS ≥ -2, suggesting that IGF-1 in young prepubertal children may not necessarily be an adequate indication of growth hormone deficiency among children of short stature [48, 56].

Additionally, we studied only prepubertal boys in order to remove any effect of sex hormones, and therefore did not take into consideration the strong influence of maturation/puberty and other biological determinants of bone strength. Additionally, including girls in a future study may help evaluate the effect of other factors such as sex on pre-pubertal bone health. Our study was also not large enough to stratify by ethnicity, which plays a role in BMD [24].

Our analysis using HR-pQCT scans was limited to peripheral sites and may not represent relationships between GHD and clinically relevant central sites. However, distal tibia parameters by HR-pQCT reflect the architecture of the central skeleton (i.e., proximal femur and lumbar spine) [57].

Despite the above limitations, our study was uniquely positioned to examine the influence of GHD on bone strength and parameters that underpin bone health in prepubertal GHD boys. HR-pQCT scans in young children can be technically difficult to perform due to the need for children to remain still and positioning problems secondary to small size. Nonetheless, we had minimal scan loss from motion artifact. The method used for supporting subjects with cushions and adding additional padding within the limb casts to mitigate limb movement, as well as focusing them with television shows worked well. Although children with GHD were found to have normal vBMD, HR-pQCT analysis revealed deficits in bone geometry that would have been missed by DXA. Short stature does not account for these deficits, as our findings persisted after controlling for height; limb length also does not account for our findings as length of radii were not significantly different between the two groups, and additionally, the same regions of interest in the radii were scanned across both groups. The findings appear to be driven primarily by a smaller cortical perimeter.

Clearly, growth hormone deficiency impacts bone size starting at a very young age. Larger studies are needed to evaluate the extent of these deficits, as well as the need for routine bone evaluation in this population. These findings lay the groundwork for investigations into the timing of earlier growth hormone replacement for prevention of these deficits and restoration of bone size, thereby enabling accrual of normal peak bone mass during adulthood.

Statement of Ethics

All procedures involved in this research study were evaluated by Columbia University's Internal Review Board. Written informed consent was obtained from parents of all subjects.

Informed consent was obtained from a parent or legal guardian and assent was obtained for children greater than 7 years of age. The study was approved by the Institutional Review Board of Columbia University Medical Center.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Tamar G. Baer was involved in all aspects of the study, including study concept, study design, recruitment of subjects, data analysis, and manuscript preparation. Sanchita Agarwal was involved in study design and specifically designed the scanning protocol for the HR-pQCT scans. She was also involved in data acquisition and interpretation, and manuscript preparation. Shaouxan Chen was involved in statistical data analysis and interpretation and manuscript preparation. Codruta Chiuzan was involved in statistical data analysis and interpretation and manuscript preparation. Aviva Sopher was involved in study design, data acquisition, specifically interpretation of pediatric DXA scans, as well as manuscript preparation. Rachel Tao was involved in data acquisition and manuscript preparation. Abeer Hassoun was involved in study design, subject recruitment, and manuscript preparation. Elizabeth Shane was involved in study concept specifically with regard to HR-pQCT protocol design, and manuscript preparation. Ilene Fennoy was involved in study design, subject recruitment, data acquisition, specifically interpretation of pediatric DXA scans, as well as manuscript preparation. Sharon E. Oberfield was involved in study concept, study design, recruitment of subjects, and manuscript preparation. Patricia M. Vuguin is the principle investigator and was involved in all aspect of the study, including study concept, study design, recruitment of subjects, data analysis, and manuscript preparation.

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