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Growth Hormone Secretion and Bone Mineral Density in Prepubertal Black and White Boys

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Abstract. Racial differences in bone mineral density (BMD) appear to account in part for racial differ-II ences in the incidence of osteoporosis and fractures. We previously reported that the greater BMD in adult blacks compared with whites is associated with a higher serum 17β-estradiol and greater secretion of growth hormone (GH) in men but not women. To determine whether these racial differences occur in prepubertal boys, we measured spontaneous overnight GH secretion, serum testosterone, 17β-estradiol, IGF-I, and IGFBP3, IGF-I/ IGFBP3 ratio, BMD of the total body, forearm, lumbar spine, trochanter, and femoral neck, and lean body mass and body fat in 14 healthy black and 16 white boys ages 6–7 years. Measurements of GH were obtained at 20-minute intervals for 12 hours. Results were analyzed by deconvolution and are expressed as mean ± SE. Whereas BMD of the hip (0.755 ± 0.020 vs 0.663 ± 0.021 g/cm^2, $P = 0.0037$), trochanter (0.617 ± 0.014 vs 0.552 ± 0.018 g/cm^2, $P = 0.0102$) and femoral neck (0.710 ± 0.018 vs 0.6381 ± 0.021 g/cm^2, $P = 0.0157$) were significantly greater in black compared with white boys, BMD of the total body (0.768 ± 0.010 vs 0.741 ± 0.012 g/cm^2, NS), forearm (0.405 ± 0.010 vs 0.380 ± 0.008 g/cm^2, NS), and lumbar spine (0.612 ± 0.013 vs 0.609 ± 0.021 g/cm^2, NS) was not different in the two groups. Stepwise regression analysis showed significant correlations between BMD and race at each skeletal site except the lumbar spine and trochanter. Deconvolution analysis revealed no racial difference in any of the GH measurements. Whereas serum testosterone, serum 17β-estradiol, and serum IGF-I were not different, serum IGFBP-3 was higher and the molar ratio of serum IGF-l/IGFBP-3 was lower in white than in black males. In summary, prepubertal BMD is higher in black than in white males at the hip, trochanter, and femoral neck, and the racial difference does not result from differences in secretion of GH.

Key words: Bone mineral density — 17β-Estradiol — Growth hormone — Insulin-like growth factor-I — Insulin-like growth factor binding protein-3 — Race — Sex hormone-binding globulin — Testosterone

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Bone mineral density (BMD) of the spine and hip is higher in black than in white men and women [1–6]. As a consequence, black adults have a lower incidence of osteoporosis and fractures than white adult [7–10]. The etiology of this difference in BMD is not clear. Growth hormone (GH) is known to influence BMD. In both children [11] and adults [12], GH deficiency is associated with low BMD, and increases in BMD were demonstrated after treatment with GH. Modest increases in BMD of the lumbar spine were observed in elderly men with low serum insulin-like growth factor-I (IGF-I) given human GH for 6 months [13]. We found racial differences in GH secretion in healthy young adult men [1] but not in premenopausal women [2].

Sex steroids also have known effects on BMD [14, 15]. Puberty is associated with significant increases in production of sex steroids [16] and GH [17] and in accrual of bone mass [8, 19]. We previously found higher BMD in black compared with white adolescent boys and girls age 7–12 years [20]. In this age range, some subjects were likely to be pubertal and others to be prepubertal.

To examine whether racial differences in BMD first emerge along with hormonal increases in puberty and whether the racial difference is present before puberty [21], we measured BMD in prepubertal black and white males. GH secretion and serum testosterone, 17β-estradiol, parathyroid hormone (PTH), IGF-I, and IGF-I binding protein-3 (IGFBP-3) also were measured.

Materials and Methods

Subjects

Fourteen black and 17 white normal boys aged 6 or 7 years and within 2 SD of mean height and weight for age were admitted to the General Clinical Research Center of the Medical University of South Carolina. The protocol was approved by the Investigational Review Board for Human Subjects, and informed consent was obtained in all subjects. All had a normal nocturnal sleep pattern, and none was taking any medi-

cation known to have effects on GH. None of them had a history of bone or renal disease. Subjects were allowed to eat *ad libitum*.

Study Design

After admission and placement of an intravenous catheter, 2-ml blood samples were obtained for GH every 20 minutes for 12 hours. A fasting blood sample was obtained the following morning for measurement of serum testosterone, 17β-estradiol, IGF-I, IGFBP-3, and immunoreactive intact PTH.

Serum Assays

Blood samples were centrifuged at 2300 rpm for 15 minutes, and plasma was removed and stored at −80°C until analyzed. Serum GH was assayed with 150 μl serum in duplicate by chemiluminescence immunometric assay [22] (Nichols Laboratories, San Juan Capistrano, CA). Sensitivity was 5 pg/ml. Cross-reactivity with human prolactin, leuteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, and chorionic gonadotropin is less than 0.01%. Inter- and intra-assay coefficients of variation were 9 and 5%, respectively. Serum IGF-I [23], IGFBP-3 [24], testosterone [25], 17β-estradiol [26], and intact PTH [27] (DiaSorin, Stillwater, MN) were measured in duplicate by radioimmunoassay.

Growth Hormone Secretion

To determine in vivo secretory measures and to estimate GH half-life, serial serum GH measurements in each subject were subjected to computerized deconvolution analysis as described previously [28, 29]. Calculated measures of interest included 12-hour integrated GH concentration, GH secretory production rate, GH secretory burst mass, GH secretory burst frequency, GH half-duration of burst, GH secretory burst mass, GH half-life, and GH mean interval.

Bone Mineral Density

BMD (g/cm^2) of the total body, total forearm, lumbar spine (L1-L4), trochanter and femoral neck, bone mineral content (BMC) (g) and bone area (cm^2) at the same sites, lean body mass (g), and percent body fat (%) were measured by dual-energy X-ray absorptiometry (DEXA) with an Hologic QDR 1000 W densitometer [1, 2]. Coefficients of variation for measurements of BMD of the spine, trochanter and femoral neck were 1.4% (n = 8), 3.3% (n = 6), and 3.1 (n = 6)%, respectively, and for phantoms of the lumbar spine, trochanter, and femoral neck they were 0.3% (n = 15), 0.6 percent (n = 15), and 2.1% (n = 15), respectively. One white male had measurements of GH and not of BMD and body composition.

Approximate Entropy

Approximate entropy (ApEn) was used as a scale- and model-independent statistic to quantity serial orderliness of regularity of the GH release process overnight. Here, as appropriate to shorter hormone time series, ApEn parameters were m = 1 and r = 20% of the intraseries SD, as described earlier [34].

Statistics

Results are reported as mean ± SEM. Student's nonpaired *t* test was used to compare GH secretory measures, BMD, BMC, body composition, serum hormones, and serum IGFBP-3 in the two groups. Multivariate stepwise regression analysis with SAS was used to evaluate determinants of GH secretion and BMD, and correlations were determined. Significance was accepted at $P = 0.05$ or less.

Table 1. Subject characteristics

Measurement	Black (14)	White (17)
Age (yr)	7.0 ± 0.2	7.1 ± 0.1
Height (cm)	124 ± 2	122 ± 2
Body weight (kg)	24.5 ± 0.7	24.0 + 0.9
BMI (kg/m^2)	16.1 ± 0.4	17.5 ± 1.1

Results are mean ± SE. ( ) is number of subjects. None of the values in the two groups were significantly different from each other

Results

Subjects

As shown in Table 1, age, height, body weight, and body mass index (BMI) were not different in the two groups.

GH Secretion

As shown in Table 2, measures of overall GH secretion including 12-h integrated GH concentration and GH secretory production rate did not differ in the two groups. Patterns of GH secretion described by GH burst amplitude, frequency, half-duration, mass, interval and half-life also were not different in the two groups.

Other Harmones

As shown in Table 3, serum IGFBP-3 was significantly greater in the white males, whereas the IGF-I/IGFBP-3 ratio was greater in the black males. Serum IGF-I, serum testosterone, serum 17β-estradiol, and serum PTH were not different in the two groups.

Bone Mineral Density

As shown in Table 4, BMD of the hip, trochanter and femoral neck was significantly higher in the black than in the white boys. BMD of the total body, forearm, and lumbar spine was not different in the two groups. Lean body mass was not different in the two groups, whereas percent body fat was higher in the white than in the black boys.

Regression Analysis-BMD

In the two groups, stepwise regression analysis showed that race correlated significantly with BMD at each of the skeletal sites except lumbar spine (Table 5). Correlation was particularly significant at the femoral neck. GH secretion, serum IGF-I, serum IGFBP-3, and IGF-

Table 2. GH secretion in the two groups

Measurement	Black (14)	White (17)	Power% [1-β]
12-h integrated GH concentration (μg/l)	2169 ± 253	1757 ± 207	95
GH secretory production rate (μg/l/127 h)	40 ± 7	29 ± 5	73
GH secretory burst amplitude (μg/l/min)	0.540 ± 0.006	0.491 ± 0.008	>99
GH secretory burst frequency (number/12 h)	5.8 ± 0.4	6.0 ± 0.3	>99
GH half-duration of burst (min)	29 ± 2	26 ± 2	>99
GH secretory burst mass (μg/l)	17 ± 2	13 ± 2	88
GH half-life (min)	16 ± 1	17 ± 1	>99
GH mean interval (min)	103 ± 6	99 ± 5	>99

Results are mean ± SE. ( ) is number of subjects. None of the values in the two groups were significantly different from each other

Table 3. Serum values in the two groups

Measurement	Black (14)	White (17)	*P* value
Serum testosterone (nmol/1)	2.8 ± 1.2	3.4 ± 1.2	NS
Serum 17β-estradiol (pmol/1)	1.6 ± 0.4	0.6 ± 0.3	NS
Serum IGF-I (ng/ml)	203 ± 26	169 ± 22	NS
Serum IGFBP-3 (μg/ml)	2.6 ± 0.1	3.0 ± 0.1	0.0449
IGF-I/IGFBP-3 (ratio)	1.6 ± 0.2	1.1 ± 0.1	0.0300
Serum PTH (pg/ml)	23 ± 2	19 ± 1	NS

Results are mean ± SE. ( ) is number of subjects

Table 4. Bone mineral density and body composition in the two groups

Measurement	Black (14)	White (16)	*P* value
BMD of total body (g/cm^2)	0.768 ± 0.010	0.741 ±0.012	NS
BMD of forearm (g/cm^2)	0.405 ± 0.010	0.380 ± 0.008	0.0619
BMD of lumbar spine (g/cm^2)	0.612 ± 0.013	0.609 ± 0.021	NS
BMD of hip (gm/cm^2)	0.755 ± 0.020	0.663 ± 0.021	0.0037
BMD of trochanter (gm/cm^2)	0.617 ± 0.014	0.552 ± 0.018	0.0102
BMD of femoral neck (g/cm^2)	0.710 ± 0.018	0.638 ±0.021	0.0157
Lean body mass (kg)	19.0 ± 0.6	18.3 ± 0.6	NS
Body fat (%)	17.0 ± 0.5	19.3 ± 0.7	0.0222

Results are mean ± SE. ( ) is number of subjects.

I/IGFBP-3 ratio correlated with BMD at a number of sites. Lean body mass correlated with BMD of the lumbar spine and hip, BMI correlated with BMD of the trochanter and femoral neck, and serum testosterone, 17β-estradiol, and PTH correlated with BMD of the femoral neck.

In the white boys, there were significant correlations between measurements of GH secretion and BMD at each site except the femoral neck where weight was borderline; between age and height and BMD of the total body and forearm; between IGF-I/IGFBP-3 ratio and BMD of the total body, lumbar spine, and trochanter; between lean body mass and BMD of the total body and trochanter; and between serum testosterone and serum 17β-estradiol and BMD of the hip and trochanter, respectively, (Table 6).

Similarly, in the black boys, there were significant correlations between measurement of GH secretion and BMD at each site except the forearm; age and BMD of the femoral neck; weight and BMD of the lumbar spine and hip; BMI and BMD of the hip; lean body mass and BMD of the lumbar spine and trochanter; serum IGF-I and total body BMD, and IGF-I/IGFBP-3 ratio and BMD of the forearm and trochanter (Table 6).

Regression Analysis-GH

In the two groups, stepwise regression analysis showed significant correlations between body fat and serum testosterone and 12-hour integrated GH concentration; body fat and GH secretory production rate, GH secretory production rate, and GH secretory burst mass; se-

Table 5. Stepwise regression analysis for BMD in all subjects

Measurement	Independent variable	Partial r^2	*P* value
Total body BMD	Race	0.1326	0.0393
	IGF-I/IGFBP-3 ratio	0.5458	0.0222
Forearm BMD	Race	0.0136	0.0490
	IGF-I/IGFBP-3 ratio	0.6363	0.0002
	GH secretory burst mass	0.0896	0.0089
	GH secretory burst amplitude	0.0067	0.0433
Lumbar spine BMD	Height	0.0602	0.0251
	Lean body mass	0.3235	0.0215
	Body fat	0.0711	0.0417
	GHhalf-life	0.0394	0.0231
	GH mean interval	0.2367	0.0202
	Serum IGF-I	0.0222	0.0294
	Serum IGFBP-3	0.2216	0.0045
Hip BMD	Race	0.0393	0.0270
	Lean body mass	0.4000	0.0086
	Serum IGFBP-3	0.1795	0.0348
Trochanter BMD	IGFBP3	0.1511	0.0316
	BMI	0.1505	0.0321
	12-h integrated GH concentration	0.1045	0.0395
Femoral neck BMD	Race	0.3694	0.0020
	BMI	0.0309	0.0254
	GH secretory burst mass	0.1088	0.0291
	Serum testosterone	0.0896	0.0164
	Serum 17β-estradiol	0.0257	0.0187
	Serum PTH	0.0086	0.0284

rum testosterone and 12-hour integrated GH concentration; serum 17β-estradiol and lean body mass and GH secretory burst and frequency;IGF-I/IGFBP-3 ratio and GH secretory burst amplitude (Table 7).

In the white boys, there were significant correlations between IGF-I/IGFBP-3 ratio and GH secretory burst amplitude and between serum testosterone and GH secretory burst frequency and GH half life. In the black boys, there were significant correlations between weight and serum IGFBP-3 and GH secretory burst frequency.

Bone Mineral Content

BMC was analyzed at the same sites as those analyzed for BMD. Like BMD, BMC was higher in black than in white boys at the same sites that differed in BMD (data not shown).

Approximate Entropy

ApEn values in the black (0.0715 ± 0.051) and white (0.710 ± 0.044) groups did not differ, indicating that process randomness or the disorderliness of GH release overnight is not quantifiably different in the two groups.

Discussion

We found greater BMD of the hip, trochanter, and femoral neck and a strong tendency for greater BMD of the forearm in black compared with white prepubertal boys as determined by DEXA. Stepwise regression analysis showed that BMD at these sites correlated with race. Since these differences in BMD are similar to several of the racial differences we had found previously in adolescent boys and young adult men [1, 2, 20], it is evident that the differences are not brought about by the effects of puberty. It is not known why there is a selectively greater BMD of the hip and femur and not lumbar spine in the black boys. Since the two groups did not differ in age, weight, height, or lean body mass, this racial difference in BMD occurs independently of these factors. The white boys had a significantly greater percent body fat that could have contributed to the difference in bone mass between the two groups. However, as our study in men found a racial difference in BMD and no racial difference in percent body fat, this may not be clinically important. Our findings of a prepubertal racial difference in BMD of the forearm that approached significance is consistent with an earlier report of greater BMD at that site assessed by single-photon absorptiometry in black compared with white children ages 1–6 years [21]. The fact that the difference was not significant in the present study may be due to the modest sample size.

When BMD was measured by CT, it was found that beginning in mid-puberty, BMD of the lumbar spine became higher in black than in white boys and girls [34]. In this study, black children had a greater cancellous bone density of the axial skeleton and similar cross-

Table 6. Stepwise regression analysis for BMD in the two groups

Measurement	Independent variable	Partial r^2	*P* value
White boys			
Total body BMD	Age	0.0013	0.0238
	Height	0.0666	0.0332
	Lean body mass	0.3837	0.0138
	GH secretory burst frequency	0.3460	0.0020
	12-h integrated GH concentration	0.0407	0.0401
	IGF-I/IGFBP-3 ratio	0.0145	0.0264
Forearm BMD age		0.0418	0.0302
	Height	0.3616	0.0177
	GH secretory burst frequency	0.3607	0.0019
Lumbar spine BMD	GH half life	0.3353	0.0237
	IGF-I/IGFBP-3 ratio	0.1885	0.0499
Hip BMD	GH secretory burst frequency	0.2947	0.0154
	GH mean interval	0.0522	0.0389
	Serum testosterone	0.1160	0.0355
Trochanter BMD	Lean body mass	0.0372	0.0303
	GH secretory burst amplitude	0.2383	0.0045
	GH secretory burst mass	0.0247	0.0187
	IGF-I/IGFBP-3 ratio	0.0109	0.0269
	Serum 17β-estradiol	0.0984	0.0090
Femoral neck BMD	Weight	0.1688	0.0586
Black boys			
Total body BMD	GH secretory burst frequency	0.1928	0.0171
	Serum IGF-I	0.5706	0.0028
Forearm BMD IGF-I/IGFBP-3 ratio		0.5104	0.0061
Lumbar spine BMD	Weight	0.3943	0.0216
	Lean body mass	0.0034	0.0120
	GH secretory burst mass	0.0282	0.0475
Hip BMD	Weight	0.4420	0.0132
	BMI	0.1857	0.0226
	GH mean interval	0.0077	0.0209
Trochanter BMD	Lean body mass	0.0372	0.0303
	GH secretory burst amplitude	0.2383	0.0045
	IGF-IGFBP-3 ratio	0.0109	0.0269
	Serum 17β-estradiol	0.0984	0.0090
Femoral neck BMD	Age	0.1699	0.0173
	GH secretory burst amplitude	0.0676	0.0183
	GH secretory burst frequency	0.3129	0.0468

sectional area of vertebral bodies, whereas black children had greater femoral cross-sectional area but similar cortical bone area and density.

In addition to race, stepwise regression analysis showed statistically significant correlations between BMD and multiple factors including measurements of GH secretion, height, weight, BMI, lean body mass, serum IGF-I, serum IGFBP-3, and circulating hormones in the two groups, separately and together.

In the present study, we found no racial difference in GH secretion. In contrast, we had previously found greater GH secretion in black compared with white young adult men [1]. 17β-Estradiol has stimulatory effects on GH secretion [16, 30]. Previous studies demonstrated progressive increases in serum 17β-estradiol during puberty and higher serum 17β-estradiol in black than in white boys only during the latter stages of puberty [31]. Therefore, the racial difference in GH secretion found in adult men may emerge first either during or after puberty in response to differences in serum 17β-estradiol.

Stepwise regression analysis showed significant correlations between measurements of GH secretion and weight, body fat, lean body mass, IGF-I/IGFBP-3, and serum sex steroids in the two groups, separately and together.

We did find racial differences in serum IGF/IGFBP-3 ratios that may indicate greater free circulating IGF-I in the prepubertal black compared with white boys, a finding also present in our study in young adult men [1]. However, with no detected racial difference in GH secretion, the etiology of the racial difference in BMD prepubertally does not appear to result from a difference in the GH axis.

Serum PTH is higher in adult black compared with white men and women as a consequence of diminished dermal production of vitamin D and reduced serum 25-hydroxyvitamin D [32, 33]. In the present study, we

Table 7. Stepwise regression analysis for GH measurements in all subjects

Measurement	Independent variable	Partial r^2	*P* value
All subjects			
12-h integrated GH concentration	Body fat	0.1871	0.0191
	Serum testosterone	0.1226	0.0411
GH secretory production rate	Body fat	0.1606	0.0312
GH secretory burst amplitude	IGF-I/IGFBP-3	0.1588	0.0323
GH secretory burst frequency	Lean body mass	0.2983	0.0022
	Serum 17β-estradiol	0.0981	0.0500
GH secretory burst mass	Body fat	0.2029	0.0142
White boys			
GH secretory burst amplitude	IGF-I/IGFBP-3	0.3979	0.0088
GH secretory burst frequency	Serum testosterone	0.2813	0.0346
GH half-life	Serum testosterone	0.2575	0.0448
Black Boys			
GH secretory burst frequency	Weight	0.5380	0.0043
	Serum IGFBP-3	2314	0.0100

found that serum PTH was higher in black than in white boys, a difference that approached but did not achieve statistical significance. This may have occurred because of the modest size of the two groups.

Previous studies in women showed that PTH-induced bone resorption is lower in black than in white women [35], a finding yet to be confirmed. It is possible, nevertheless, that skeletal resistance to PTH is a contributing factor to the greater BMD not only in black compared with white women but in black children and men as well. Interestingly, in our earlier studies we found lower urinary phosphorus in black compared with white men and women on comparable intakes of calcium and phosphorus despite higher serum immunoreactive PTH and urinary cyclic adenosine monophosphate (cyclic AMP) in the blacks [32]. Serum phosphorus was not different in the two groups. Whether there is relative resistance of the kidney to the phosphaturic effect of PTH in blacks is not known. If so, it would appear that the resistance is to cyclic AMP since the nucleotide mediates the phosphaturic action of the 10 hormone.

In summary, racial differences in BMD of the hip, trochanter, and femoral neck, as assessed by DEXA analysis, occurs prepubertally in boys. In contrast, the racial differences in serum 17β-estradiol and GH secretion found in adult men do not begin prepubertally.

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