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Prepubertal Girls with Premature Adrenarche Have Greater Bone Mineral Content and Density Than Controls

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Abstract

Body composition in premature adrenarche (PA) has not been described. We hypothesized that the increased adrenal androgens in PA would have a trophic effect on lean body components. We studied 14 PA subjects and 16 controls, all pre-pubertal Hispanic girls. The body composition parameters tested included height, weight, bone mineral density (BMD), bone mineral content (BMC), nonbone fat-free mass, total body potassium, total body water, and extracellular water. Bone age was determined in all PA subjects.

Compared with controls, PA subjects had significantly higher BMC ($P = 0.02$) and BMD ($P = 0.03$) when adjusted for age, weight, height, and fat mass, but were not different in the following lean body components: fat-free mass, total body potassium, total body water, and extracellular water. There was no difference in BMD or BMC between the PA subjects with and without advanced bone age.

These data suggest a specific effect of PA on bone mineral, but not on other lean body components. The absence of a correlation between bone age and bone mineral in this small group leads us to propose there are separate promoters of bone age advancement and bone mineral accrual. Candidate hormones for these processes include adrenal androgens, E, and IGF-I. The findings of this study suggest that hormonal alterations associated with PA affect bone mineral accrual and may elucidate the mechanisms involved in this process.

Precocious or premature pubarche is defined as the appearance of pubic hair before 8 yr in girls and 9 yr in boys unaccompanied by signs of true puberty, such as breast development in girls and testicular enlargement in boys. Premature adrenarche (PA) is the term used for individuals with premature pubarche whose adrenal androgens are at the Tanner stage 2 level of puberty and in whom enzymatic defects of steroidogenesis, precocious puberty, and adrenal or gonadal malignancy have been ruled out (1, 2).

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PA is caused by an early isolated maturation of the zona reticularis of the adrenal cortex resulting in increased adrenal androgen secretion for chronological age (3-6). However, some individuals with PA have normal androgen levels but increased peripheral sensitivity to androgens (7). Tall stature and advanced skeletal maturation may be present at diagnosis (4, 5, 8). Although PA was originally thought to be a benign and self-limited physiological process, recent work suggests that girls with PA are more likely to develop polycystic ovary syndrome, hyperinsulinism, and dyslipidemia (9-13).

Recently, there have been numerous studies that describe the effects of androgens and estrogens (E) on lean body components (14-23). Components of the lean body mass that are positively affected by androgens include bone, nonbone fat-free mass, total body potassium, and total body water. Evaluation of body composition in girls with PA may suggest mechanisms responsible for bone mineral and lean body mass accrual. To our knowledge the effects of relative hyperandrogenism on lean body mass components in prepubertal girls with PA have not been reported, although skeletal maturation, as assessed by x-ray of the hand and wrist, to determine bone age has been well described. The goals of this study were 1) to determine whether prepubertal girls with PA have differences in bone mineral content (BMC) and bone mineral density (BMD) compared with prepubertal girls who do not have PA; 2) to test whether bone age correlates with bone mineral status in prepubertal girls with PA; and 3) to evaluate the relationship of PA and lean body components in prepubertal girls.

Subjects and Methods

Subjects

The study group consisted of 14 prepubertal Hispanic girls primarily of Dominican and Puerto Rican origin with PA recruited from the pediatric endocrinology service at Children's Hospital of New York at Columbia-Presbyterian Medical Center. Informed consent was obtained from a parent or guardian and assent was obtained from each subject above the age of seven. The protocol was approved by the Institutional Review Boards of St. Luke's-Roosevelt Hospital Center and of Columbia-Presbyterian Medical Center. The diagnosis of PA was made on a clinical basis. The criteria for entry into the study were 1) onset of pubic hair before the age of 8 yr, 2) no clitoromegaly, 3) Tanner stage 1 breasts on physical exam, and 4) no evidence of 21-hydroxylase deficiency or other adrenal or gonadal disorder by hormonal analysis.

Control subjects were 16 Hispanic girls primarily of Dominican and Puerto Rican origin who were participants in the Pediatric Rosetta Project, a cross-sectional study of pediatric body composition in normal children. All controls were Tanner stage 1 for both breasts and pubic hair. Informed consent was obtained from a parent or guardian, and assent was obtained from each subject above the age of 7 yr. The Pediatric Rosetta Project was approved by the Institutional Review Board of St. Luke's-Roosevelt Hospital Center.

Pubertal and clinical assessment

Pubertal and clinical assessments of PA subjects were performed at the pediatric endocrinology clinic. Breasts and pubic hair were assessed by the criteria of Tanner. Skeletal

maturation was determined by the standards of Greulich and Pyle by one observer (24). Those subjects with a bone age z-score greater than or equal to 2 SD above the mean for age were considered to have advanced bone age. An early morning fasting 17-hydroxyprogesterone measurement was obtained for all subjects. Subjects with a value greater than 100 ng/dl underwent ACTH stimulation testing.

Pubertal assessment of the control subjects was performed by the Pediatric Rosetta Project nurse or pediatric endocrinologist by the criteria of Tanner. Skeletal maturation was not determined in these subjects.

Body composition assessment

Studies were performed at least 1 h after a meal. Body weight was measured to the nearest 0.1 kg on a balance-beam scale (Weight Tronix, New York, NY), and height to the nearest 0.1 cm using a wall-mounted stadiometer (Holtain, Crosswell, Wales).

Whole body dual energy x-ray absorptiometry (DXA) scans were performed using Lunar Corp. models DPX and DPXL with pediatric software version 3.8G (Lunar Corp., Madison, WI) (25). Each scan provided estimates of nonbone fat-free mass and fat mass in kilograms, percent body fat, total BMC in grams, and total body BMD in grams per cm^2. The technical error for measuring fat mass in adults by DXA in our laboratory is 3.3% (26). The percent coefficient of variation for repeated BMC measurements by whole body scanning in humans is approximately 1.5% (25). Repeated studies of a phantom in our unit revealed a coefficient of variation of 0.6% for BMC. The coefficient of variation for repeated BMD measurements in adult subjects in our laboratory is 0.5% (26). An anthropomorphic spine phantom made up of calcium hydroxyapatite embedded in a 17.5 × 15 × 17.5-cm Lucite block was scanned with both DXA instruments for quality control each morning before subject evaluation. The phantom was also scanned immediately before and after all DXA system manufacturer maintenance visits. The measured phantom BMD was stable throughout the study period at 1.166 -1.196 g/cm^2. Ethanol and water bottles (8-liter volume), simulating fat and fat-free soft tissues, respectively, were scanned as soft tissue quality control markers monthly. The range in measured r values over the study period was 1.255–1.258 (coefficient of variation, 0.127%) and 1.367 - 1.371 (coefficient of variation, 0.103%), for ethanol and water, respectively.

Total body potassium (milliequivalents) was measured in a 4-pi liquid scintillation ^{40}K whole body counter calibrated with ^{40}K standard bottles. The reproducibility for total body potassium in children with a weight of 18 kg is 2.2% and improves with increasing weight (27, 28).

Total body water (liters) was measured by dilution of deuterium (D_2O) given orally. The technical error of total body water estimate in adults is 2.1% (29). Extracellular water (liters) was measured by dilution of sodium bromide given orally and measured by bromide ion chromatography. The technical error of extracellular water estimate in adults is 2.9% (29).

Statistical analysis

An analysis of covariance was performed to compare body composition results of the 14 subjects with PA and the 16 controls. Variables tested were BMC, BMD, nonbone fat-free mass, total body potassium, total body water, and extracellular water. The BMC values were transformed to log (BMC) and the BMD values to 1/BMD for analysis. These transformations were determined from the Box-Cox family of transformations (30). The covariates used in the analysis were age, weight, height, and fat mass (kilograms). An analysis of covariance adjusting for age was performed to compare BMC and BMD in PA study subjects with advanced bone age (n = 10) to those without advanced bone age (n = 4), using BMC as log (BMC) and BMD as 1/BMD.

All statistical calculations were performed using the STATA version 6.0 statistical software package for personal computers. The level of significance was 0.05 for all statistical tests of hypothesis.

Results

Subject characteristics are presented in Table 1. The average bone age z-score for PA subjects was 2.53 (range, 0.72–4.32). Ten subjects had advanced bone age (z-score, ≥2), and four subjects did not. Bone mineral and body composition results are presented in Table 2.

Prepubertal girls with PA had significantly higher BMC and BMD than prepubertal controls when adjusted for age, weight, height, and fat mass. The adjusted difference in BMC as log (BMC) was 0.084 ($P = 0.02$), and that in BMD as 1/BMD was 0.056 ($P = 0.03$).

The difference in bone mineral variables between girls with PA with and without advanced bone age was not significant. The adjusted difference in log (BMC) was 0.181 ($P = 0.11$), and that in 1/BMD was 0.0603 ($P = 0.20$).

There were no differences between results in girls with PA and controls in the following lean body components: non-bone fat-free mass by DXA ($P = 0.76$), total body potassium ($P = 0.12$), total body water ($P = 0.36$), and extracellular water ($P = 1.00$).

Discussion

In this cross-sectional study we have demonstrated that prepubertal girls with PA have significantly greater BMD and BMC than prepubertal girls without PA. Our analysis suggests that this effect is independent of bone age. In this small study other components of lean body mass were not significantly different from controls, suggesting an effect of PA that is specific to bone.

Studies in adults have demonstrated increased BMD in hirsute women with and without polycystic ovarian syndrome compared with nonhirsute women. High androstenedione is a frequent finding in hirsute women, but correlations between BMD or BMC and androstenedione have been inconsistently demonstrated (15, 16). In a study of two prepubertal and eight pubertal girls with complete androgen insensitivity syndrome, BMD was significantly lower than that of controls (17), suggesting a role for androgens in bone

mineral accrual. It is possible that the higher bone mineral observed in prepubertal girls with PA in the current study reflects the presence of increased levels of androgens compared with normal controls.

In vitro studies have demonstrated that bone has AR that are responsive to the adrenal androgen dehydroepiandrosterone (DHEA), although to a lesser degree than to the gonadal androgen dihydrotestosterone (DHT) (31, 32). These studies demonstrated that DHT and DHEA act directly on osteoblasts by binding to AR, with subsequent stimulation of growth and differentiation (32), and that the effect of DHEA was independent of conversion to DHT (31). These findings support the possibility that the continuous exposure to elevated levels of adrenal androgens in prepubertal girls with PA could be responsible for the observed increased bone mineral in the absence of a significant contribution of gonadal androgens.

Both bone and nonbone lean body mass have been shown to be positively affected by T (14). Our results suggest that the hyperandrogenism associated with PA has a similar effect on bone as T, but not on muscle mass. These findings suggest that perhaps the role of E on bone should be considered in our subjects. The effects of E on bone include linear growth, skeletal maturation, accrual of bone mass, and bone mass maintenance and repair (18-23). E2 may exert significant biological effects below the detection limit of standard RIAs (33). E has been shown to have a more potent effect on bone mineral than androgens and to be important in both males and females (19). Studies of males affected with aromatase deficiency and ERα resistance emphasize the complexity of the processes of bone maturation and accrual, which include multiple mechanisms (19, 20).

The prepubertal growth spurt and the advancement of bone age observed in PA are additional evidence that E may play an important role in the pathophysiology of PA (8, 33). It is unclear why only some girls with PA have advanced bone ages, but it appears that growth spurt and bone age advancement are dependent on the actions of E (19-22), possibly due to peripheral conversion of androgens to E (23), cross-activation of ER by androgens (18), or priming of the ovaries in response to adrenarche.

Both IGF-I and insulin may contribute to ovarian and adrenal hyperandrogenism (34). Prepubertal girls with PA have been demonstrated to have higher IGF-I and free IGF-I levels and lower IGF-binding protein-1 levels than unaffected controls suggesting increased IGF-I activity (35, 36). IGF-I has also been shown to positively influence BMC and BMD (37). It is proposed that higher levels of IGF-I in African Americans may contribute to their higher BMD compared with other ethnic groups (37). In contrast, IGF-I does not appear to affect skeletal maturation. In a small study of healthy prepubertal girls bone age was found to be independent of IGF-I, whereas both bone age and weight were significant covariates for DHEA sulfate levels (38). Together these findings potentially explain the observed discordance between bone mineral accrual and bone age in prepubertal girls with PA in the current study and suggest that IGF-I may contribute to the higher BMD and BMC seen in our subjects.

This report demonstrates a significant effect of PA on bone mineral mass without an effect on other lean body components in a small group of prepubertal Hispanic girls with PA

compared with controls. A distinction between hyperandrogenism associated with PA and the androgen effect resulting from T administration is suggested by the lack of an effect on muscle and other lean body components in this small study group. These findings suggest that the hyperandrogenism observed in PA may directly or indirectly affect bone mineral mass. It is also possible that higher levels of IGF-I, free IGF-I, or IGF-I activity may contribute to these findings. Although the subjects in our study were prepubertal, it is possible that they had higher circulating levels of E than normal prepubertal controls. The absence of a correlation between bone age advancement and bone mineral mass in this small study group leads us to propose that separate mechanisms may be responsible for these processes. These findings need to be confirmed in a larger population. Additionally, it would be interesting to follow these girls longitudinally through puberty to determine whether their skeletal advantage is maintained.

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Abbreviations

BMC	Bone mineral content
BMD	bone mineral density
DHEA	dehydroepiandrosterone
DHT	dihydrotestosterone
DXA	dual energy x-ray absorptiometry
PA	premature adrenarche

TABLE 1

Characteristics of subjects with premature adrenarche and controls

	Premature adrenarche	Controls
N	14	16
Age (yr)	7.0 ± 1.0 (5.1–8.6)	7.9 ± 1.2 (5.6–9.4)
Age at bone age (yr)	6.8 ± 1.0 (4.9–8.5)	NA
Bone age (yr)	8.2 ± 1.6 (5.8–12.0)	NA
Ht (cm)	126.8 ± 9.8 (111.8–143.1)	125.0 ± 8.2 (108.3–140.2)
Wt (kg)	36.9 ± 15.2 (20.0–72.8)	29.8 ± 9.7 (18.0–56.8)
Fat (kg)	13.8 ± 9.9 (2.9–36.9)	8.9 ± 6.8 (1.8–27.9)

NA, Not measured. Values are the mean ± SD, with the range in *parentheses*.

TABLE 2

Bone mineral and body composition results in premature adrenarche and control subjects

	Premature adrenarche	Controls
BMC (g)	1104 ± 308 (763–1862)	950 ± 204 (671–1518)
BMD (g/cm^2)	0.898 ± 0.097 (0.796–1.173)	0.849 ± 0.061 (0.751–1.017)
Total body potassium (mEq)	1118 ± 274 (655–1618)	1101 ± 192 (765–1522)
Total body water (liter)	17.0 ± 4.4 (11.6–26.6)	15.7 ± 3.0 (11.7–22.8)
Extracellular water (liter)	8.3 ± 2.4 (5.3–12.9)	7.2 ± 1.9 (5.4–11.8)
Nonbone fat-free mass by DXA (kg)	23.1 ± 5.6 (16.1–35.9)	20.8 ± 3.3 (14.0–28.9)

BMC, Bone mineral content; BMD, bone mineral density; DXA, dual energy x-ray absorptiometry. Values are the mean ± SD, with the range in *parentheses*.