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Racial difference in circulating sex hormone–binding globulin levels in prepubertal boys

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Abstract

Racial differences in disease risk (eg, osteoporosis, metabolic cardiovascular syndrome, and prostate cancer) may arise partly on a hormonal basis. While reports of racial differences in gonadal steroid hormone levels in middle-aged men have produced conflicting results, there is evidence that high sex hormone–binding globulin (SHBG) and estradiol levels are more common among young adult African American men than white men. To determine whether this difference relates to pituitary-testicular functioning or to other factors, we conducted a cross-sectional study of 47 healthy prepubertal African American and white boys aged 5 to 9 years at the time of their annual school physical examination. Height, weight, blood pressure, waist and hip circumference, and Tanner staging were determined, and a fasting blood sample was obtained. The African Americans studied were slightly older than the whites (mean ± SD, 82.4 ± 15.0 vs 70.5 ± 10.3 months, $P = .003$). African Americans were also slightly taller and heavier and had a lower waist-to-hip ratio, but these differences could be explained by the difference in age. Mean SHBG levels were 25% higher ($P = .15$) in African Americans than in whites (197 ± 104 vs 157 ± 79 nmol/L), and when adjusted for age, values were 46 nmol/L higher among African Americans. The fifth quintile for SHBG (values > 245 nmol/L) included 1 (4.2%) of 24 whites and 8 (35%) of 23 African Americans studied ($P = .003$). There was no significant correlation between age, body mass index, waist circumference, or fasting insulin and SHBG. Total testosterone, the free androgen index, and dehydroepiandrosterone increased with age in both groups, but after adjusting for age, no racial differences were found. Estradiol, estrone, and inhibin B levels, as well as systolic and diastolic blood pressures, were also comparable in both groups. We conclude that high levels of SHBG are more common among African American than in white boys and hypothesize that this difference and its effect on the ratio between bound and free steroid hormones may contribute to racial differences in disease risk in adult men.

1. Introduction

Sex hormone–binding globulin (SHBG) transports testosterone and other steroids in the circulation [1-3] and is an important determinant of the total testosterone level in adult men [4]. The prevailing view is that SHBG reduces the cellular uptake of steroid hormones from the plasma compartment and negatively regulates their availability to target cells [5,6]. On the other hand, experiments using prostate epithelium and stroma imply a paracrine function of SHBG as an androgen receptor coactivator [7,8]. Either by binding sex steroids or through direct actions, SHBG is important in health and disease.

The regulation of SHBG in plasma is complex. SHBG is regulated developmentally, with a pronounced decline from infancy to puberty in both sexes [9] and an increase in men as they age [4]. SHBG is also under metabolic control. SHBG is inversely proportional to body mass index (BMI) [10] and to the amount of body fat [11,12], and body composition and SHBG are linked in part through insulin. Plasma fasting insulin levels correlate negatively with SHBG levels [13], and lowering insulin levels with diazoxide increased plasma SHBG in men [14] as in obese women with polycystic ovary syndrome [15]. Insulin reduces SHBG gene expression and protein secretion by HepG2 hepatoma cells [16,17]. SHBG is also increased by thyroxine and estrogens and is decreased by androgens, glucocorticoids, and growth hormone [18], although the mechanisms for these effects are not well established.

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In a previous study [19], we found that high SHBG levels were more common among young adult African American than white men living in western Pennsylvania and were partly linked to smaller waist circumference and lower fasting insulin levels. Higher mean SHBG levels were found by Gapstur et al (personal communication) in African American men aged 20 to 23 years who were enrolled in the multicenter Coronary Artery Risk Development in Young Adults study [20], and slightly higher (5%, P = NS) mean levels were found by Ross et al [21] among young adult African American men living in southern California. By middle age, there may be no racial difference in SHBG [20,22,23].

Racial differences in SHBG could occur because of genetic or lifestyle factors, or differences in functioning of the hypothalamic-pituitary-testicular unit. Accordingly, results in prepubertal boys, in whom gonadal function is quiescent, are of interest, but information is limited. A study appeared recently of 19 African American and 29 white prepubertal boys in whom no significant racial difference in serum SHBG was found [24], but those boys ranged in age from 4 to 11 years and were defined as prepubertal based on a questionnaire. In the present study, we measured SHBG and sex steroid levels in healthy prepubertal African American and white boys aged 5 to 9 years at the time of a routine physical examination and related these values to body composition to learn whether differences exist in SHBG in childhood that might contribute to racial differences in disease risk in adult men.

2. Materials and methods

2.1. Study design

A cross-sectional study was conducted in a general pediatric clinic of 48 African American and white prepubertal boys who were older than 5 but less than 9 years and were being seen for a routine school physical examination. No subject had a chronic illness or was taking any regular medication. After obtaining informed consent from the subject and parent or legal guardian, a physical examination that included height, weight, blood pressure, waist and hip circumference, and Tanner staging [25] was performed. Subjects were asked to fast overnight, and a blood sample was obtained between 0830 and 1500 hours for the measurement of SHBG, testoterone, estradiol, estrone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), inhibin B, dehydroepiandrosterone (DHEAS), and insulin.

2.2. Immunoassays

The level of SHBG in serum was measured using an enzyme-linked immunosorbent assay (ELISA) from Diagnostic System Laboratories (DSLabs, Webster, Tex). The standard curve ranged from 6.5 to 376 nmol/L. The within-assay coefficient of variation across a range of values was less than 10%. All samples were run in one assay to eliminate any effect of between-assay variation. Testosterone was measured using a radioimmunoassay (RIA) kit from Diagnostic Products (Los Angeles, Calif). The standard curve ranged from 5 to 1600 ng/dL, and the minimal detectable dosage, equivalent to 2 SD difference from the zero calibrator, was 3.1 ng/dL. The within-assay coefficient of variation of quadruplicate determinations of a pool with a potency of 29 ng/dL was 6%. All samples were run in one assay. Estradiol was measured using an iodine I 125 estradiol assay kit (Pantex, Santa Monica, Calif) after extraction of 500 μL of serum with 5 mL hexane/ethyl acetate (3:2 vol/vol). The minimal detectable dosage was 5 pg/mL. Estrone was measured using an RIA from DSLabs. The standard curve was extended to 2.5 pg/mL, and the minimal detectable dosage was less than 3 pg/mL. The within-assay coefficient of variation was less than 6%. LH and FSH were measured using immunoradiometric assay kits from DSLabs. Inhibin B was measured using an ELISA kit from Serotec (Washington, DC). Dehydroepiandrosterone was measured with the DPC Coat-A-Count RIA kit (Diagnostic Products). Insulin was measured with an ELISA kit from DSLabs. The standard curve ranged from 2.5 to 100 μU/mL, and the minimal detectable dosage was 1.5 μU/mL.

2.3. Data analysis

One of the 24 African American boys had a BMI of 27.9 kg/m^2, a value that was 3.2 SD above the mean and was clearly an outlier. This subject was excluded. Data are presented as the mean $\pm$ SD. Student t tests were performed using SAS PROC TTEST (SAS Institute, Cary, NC). Multiple regression analyses and analyses of covariance using ethnicity and adjusting for the subjects' age in months were also performed using SAS PROC GLM. This technique adjusts the results to values that would have occurred if the mean age for each group had been equal to the mean age for the sample as a whole. Further, to examine race as a predictor of circulating SHBG levels, the prevalence of each racial group was analyzed by χ^2 testing of SHBG quintiles, defined as < 105, 105-145, 145-178, 178-254, and > 245 nmol/L.

3. Results

The clinical characteristics of the study population are summarized in Table 1. All boys had testicular volumes of 3 cm^3 or less, based on comparison with an orchidometer, and no subject had visible terminal pubic hair. Although the study subjects ranged in age from 5 to < 9 years, the mean age of the African Americans we recruited was 11.9 months older than the whites (P = .003), and their heights and weights were correspondingly greater. Although the BMI was comparable in both groups, the waist-to-hip ratio was slightly lower in African Americans than in whites. After the data were adjusted for age, however, no racial differences were evident.

Table 1
Clinical characteristics of the study population

Variable	African Americans (n = 23)	Whites (n = 24)	*P* (2-sided)
Raw means			
Age (mo)	82.4 ± 15.0	70.5 ± 10.3	.003
Height (cm)	119.0 ± 7.7	114 ± 5.9	.02
Weight (kg)	24.47 ± 5.49	21.13 ± 4.43	.03
BMI (kg/m^2)	17.1 ± 2.4	16.1 ± 2.0	.12
Waist (cm)	21.2 ± 2.2	20.8 ± 1.9	.49
Hip (cm)	24.6 ± 2.9	23.2 ± 2.1	.08
Waist-to-hip ratio	0.87 ± 0.05	0.90 ± 0.04	.03
SBP (mm Hg)	92.2 ± 11.7	91.3 ± 11.2	.79
DBP (mm Hg)	54.1 ± 8.9	56.8 ± 8.8	.30
Age-adjusted means			
Age (mo)	76.3	76.3	NA
Height (cm)	116.5	116.3	.90
Weight (kg)	22.91	22.63	.82
BMI (kg/m^2)	16.7	16.5	.75
Waist (cm)	20.8	21.2	.63
Hip (cm)	23.8	23.9	.92
Waist-to-hip ratio	0.88	0.89	.44
SBP (mm Hg)	90.3	93.1	.43
DBP (mm Hg)	53.0	57.9	.08

Data are mean ± SD or adjusted mean from the analysis of covariance. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; NA, not applicable.

Mean SHBG levels were 25% higher among African Americans (197 ± 104 vs 157 ± 79 nmol/L, $P = .15$), and when adjusted for age, the difference increased to 46 nmol/L (Table 2). To determine whether high levels of SHBG are more common among African American than among white boys as in our previous study of young adults [19], the results for SHBG were divided into quintiles. As illustrated in Fig. 1, among those boys in the highest quintile for SHBG (> 245 nmol/L), 89% were African Americans. According to this analysis, 8 (35%) of 23 African

Table 2
Hormone levels in African American and white boys

	African Americans (n = 23)	Whites (n = 24)	*P* (2-sided)
Raw means			
SHBG (nmol/L)	197 ± 104	157 ± 80	.15
Testosterone (ng/dL)	7.11 ± 5.2	4.1 ± 3.4	.02
Free androgen index (×10^3)	1.91 ± 2.43	1.10 ± 1.07	.16
DHEAS (μg/dL)	29.7 ± 22.6	17.8 ± 19.2	.06
Estrone (pg/mL)	28.2 ± 19.0	20.9 ± 22.0	.23
Estradiol (pg/mL)	5.5 ± 1.5	5.1 ± 1.2	.24
Inhibin B (pg/mL)	82 ± 34	77 ± 41	.66
Age-adjusted means			
SHBG (nmol/L)	200	154	.13
Testosterone (ng/dL)	6.4	4.8	.24
Free androgen index (×10^3)	1.66	1.34	.59
DHEAS (μg/dL)	25.3	22.0	.59
Estrone (pg/mL)	25.9	23.2	.68
Estradiol (pg/mL)	5.5	5.1	.34
Inhibin B (pg/mL)	80	79	.93

Data are mean ± SD or adjusted mean from the analysis of covariance.

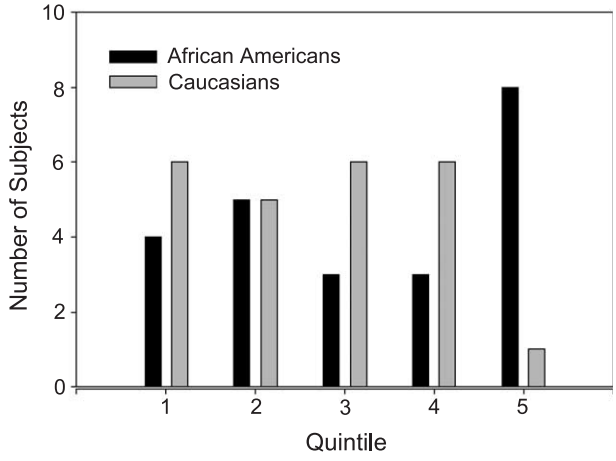

Fig. 1. Distribution, by quintiles, of serum levels of SHBG in African American and white boys. SHBG quintiles: 1 indicates < 105 nmol/L; 2, 105-145 nmol/L; 3, 145-178 nmol/L; 4, 178-254 nmol/L; 5, > 245 nmol/L.

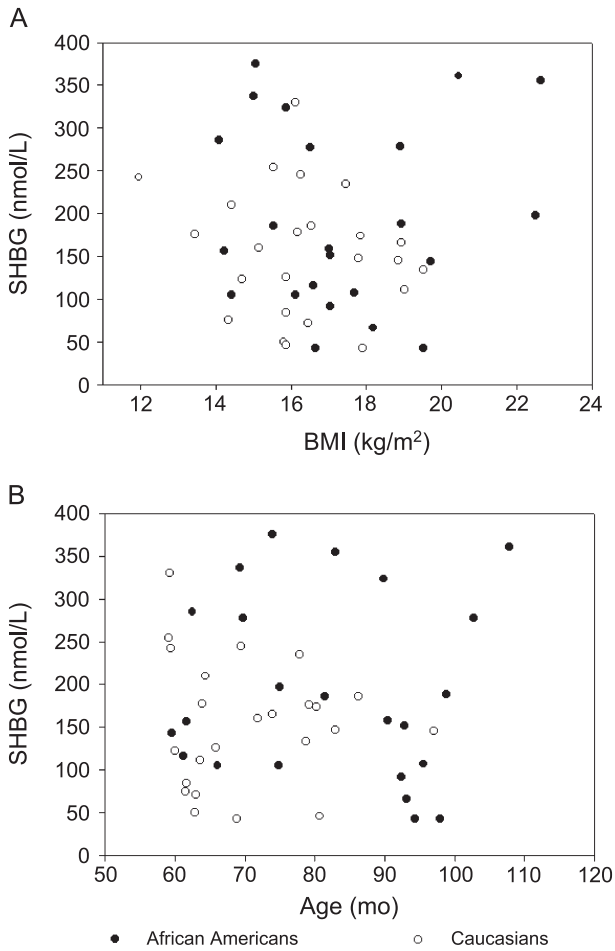

Fig. 2. A, Relation between BMI and SHBG among prepubertal African American and white boys. B, Relation between age and SHBG among prepubertal African American and white boys.

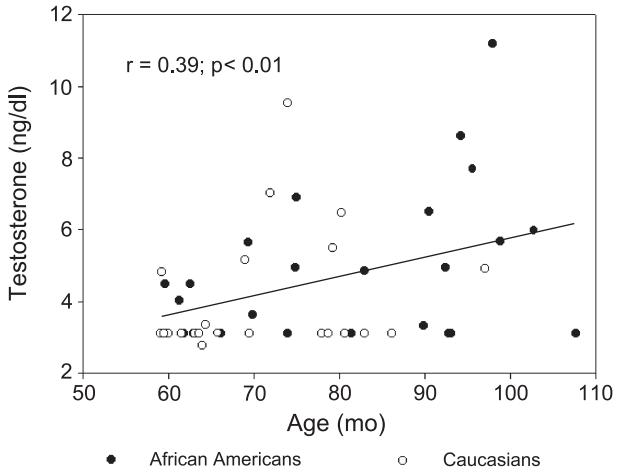

Fig. 3. Regression coefficient relating age to total testosterone among prepubertal boys. Values below 3.1 ng/dL were set at this limit of detection for analysis.

Americans compared with 1 (4.2%) of 24 whites studied had values in the fifth quintile ($P = .004$).

SHBG was independent of BMI (Fig. 2A) as well as of waist circumference (not shown). SHBG was also independent of age (Fig. 2B). Twenty-five subjects fasted overnight for the blood sampling. These boys were divided into 2 groups, again based on a level of SHBG above (n = 7) or below (n = 18) 245 nmol/L. Fasting insulin levels were comparable in the 2 subgroups (4.82 ± 1.06 vs 3.75 ± 0.39 μU/mL, $P = .11$).

The results of additional measurements are found in Table 2. The total testosterone level was 71% higher in African Americans. Likewise, the level of DHEAS was 67% higher in African Americans. However, these differences were explained by the older age for this group of subjects. As shown in Fig. 3 for the groups combined, total testosterone increased with increasing age ($r = 0.45$, $P < .01$). Total testosterone was positively correlated with DHEAS ($r = 0.44$, $P < .01$) but was independent of SHBG ($r = 0.05$, $P > .05$). Serum levels of estradiol, estrone, and inhibin B were similar in the 2 groups, and LH and FSH levels were less than 0.1 mIU/mL in all subjects. Finally, there was no significant increase in inhibin B with increasing age ($r = 0.15$, $P > .05$).

4. Discussion

We found that high levels of SHBG are more common among healthy African American prepubertal boys than among white boys. This finding is strikingly similar to our previous results in healthy male college students aged 18 to 21 years who were living in western Pennsylvania [19]. In that study population, 80% of the men in the highest quintile for SHBG were African American. In the current study of prepubertal boys, mean SHBG levels were 25% higher among African Americans, but the P value for the between-group difference was .15. From this and our previous study [19] as well as the work of others [20,21], we conclude that young men with high levels of SHBG are much more likely to be African American than white, although there is overlap in the range of values for the 2 groups as a whole.

High SHBG levels in boys could not be explained by age, BMI, or waist circumference, or by lower fasting insulin levels. In adult men, fat mass is inversely related to SHBG [12]. While BMI and weight circumference were unrelated to SHBG in this study, studies using computerized tomography have found less intra-abdominal adipose tissue in African American than white boys [26,27], and it remains possible that high SHBG levels are due to a racial influence in body composition. A larger and more detailed study is needed. Insulin is one link between visceral obesity and SHBG, and our negative results for insulin must also be interpreted cautiously because the boys were studied as outpatients and their fasting status was not assured, and glucose-stimulated insulin was not studied. Sex-specific familial correlations [28] and findings in monozygotic and dizygotic twin adult men [29] reveal that SHBG is genetically regulated. A polymorphism in the SHBG coding sequence that produces an electrophoretic variant that is cleared more slowly than the wild type has been identified [30,31] and could be more prevalent among African Americans. A second potential genetic mechanism for high SHBG follows from the finding that fewer TAAAA repeats in the SHBG promoter were associated with lower transcriptional activity of a luciferase reporter construct in HepG2 cells, with a tendency toward lower SHBG levels in a small number of healthy men [32], although not in European women [33,34].

It is interesting to speculate that high levels of SHBG beginning in childhood contribute to disease risk among African American men. SHBG may coactivate the androgen receptor in prostate through cyclic adenosine monophosphate–dependent protein kinase A signaling [35] and thereby contribute to the increased risk for prostate cancer among African Americans [36]. SHBG levels are reduced in men with the metabolic cardiovascular syndrome [37], and high SHBG may relate to the lower risk for this syndrome among African American men [38] that begins in adolescence [39].

A high level of SHBG would tend to reduce the fraction of circulating testosterone that is free or albumin bound. At puberty, reduced “bioavailable” testosterone would be expected to stimulate gonadotropin-releasing hormone and increase circulating LH and FSH levels, as occurs in hyperthyroid men whose SHBG levels are markedly elevated [40]. The SHBG-induced rise in LH and FSH would stimulate testicular aromatase [41-43] to produce higher circulating estradiol levels, a finding that has been reported in several studies of young adult African American men [22,44,45]. Our findings of comparable circulating estradiol and estrone levels in African American and white boys agree with previous results in prepubertal boys [46,47]

and imply that higher levels of estradiol in young adult African American men are dependent on gonadotropin. It is interesting to speculate that higher estradiol levels contribute to the greater increase in bone mass that occurs during puberty in African Americans [48] and to their reduced fracture risk in adulthood [49-51]. Estrogens also influence vascular reactivity and function as an anti-atherosclerotic agent [52], and thus SHBG could contribute to the notion of reduced risk for atherosclerotic heart disease [53] among African Americans.

The lack of relationship between age and SHBG among boys aged 5 to 9 years is consistent with the data in a previous cross-sectional study in which the decline from infancy to adulthood can be attributed to differences between ages 1 and 5 years and between ages 11 years and adulthood [9]. We observed a rise in DHEAS and testosterone levels with increasing age, with a trend to higher levels ($P = .06$) among African Americans because of their slightly older age. The rise in plasma DHEAS with age was expected [54]. Although there are few studies of age-related changes in testosterone among prepubertal boys, Belgorosky and Rivarola [55] reported that total and non–SHBG-bound testosterone increase with age among prepubertal boys aged 0.5 to 14 years, whereas 2 smaller studies found no age-associated increases [56,57]. Admittedly, the low levels of testosterone in sera in prepubertal boys make accurate detection difficult [58]. The source of the testosterone in prepubertal boys may be from the adrenal cortex, because DHEAS and testosterone levels were positively correlated, or from the testes, because the testosterone in spermatic vein blood in boys undergoing orchidopexy exceeds circulating levels, implying testicular testosterone secretion [59]. Total testosterone was unrelated to SHBG, as reported previously for boys [60], presumably because only a small portion of SHBG binds testosterone given the low levels of the androgen in serum.

From this cross-sectional study, we conclude that high levels of SHBG occur more often among African American than among white boys and hypothesize that high SHBG levels in childhood and young adulthood [19] contribute to disease risk as African American men grow older. Larger and prospective studies are needed to confirm these hypotheses.

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