Testosterone, Sex Hormone-Binding Globulin, and Body Composition in Young Adult African American and Caucasian Men

Stephen J. Winters, Adam Brufsky, Joel Weissfeld, Donald L. Trump, Mary Ann Dyky, and Venus Hadeed

This study examined the diurnal variation in circulating total and free testosterone and sex hormone-binding globulin (SHBG) levels in young adult African American and Caucasian men in order to investigate whether there are differences in the secretion of these plasma hormones in populations at different risks of developing prostate cancer as they age. A significant and similar diurnal rhythm for total and free testosterone was found for both groups. Serum levels of total testosterone were 29.4% and 23.9% lower at 8:00 PM than at 8:00 AM in African American and Caucasian men, respectively. Significantly higher serum levels of total testosterone ($P < .01$) and SHBG ($P < .02$) were found in the African American than in the Caucasian men in both the morning and evening, whereas free testosterone levels were similar in both groups. The higher SHBG levels appear to have an environmental/metabolic basis in that the waist circumference, waist-to-hip ratio, and fasting insulin concentration were lower ($P < .05$) in African Americans than in Caucasians. In summary, these data indicate that racial differences in central adiposity in men are established in early adulthood and influence circulating SHBG and thereby testosterone levels. In light of the findings by others that SHBG increases cyclic adenosine monophosphate (cAMP) production in the prostate and that cAMP-dependent protein kinase A is a coactivator of the androgen receptor, these studies provide a possible mechanism by which circulating androgens may contribute to the increased risk for prostate cancer among African American men.

THE HIGHER RATE OF prostate cancer among African American men compared with Caucasians has been proposed to have a hormonal basis.[1-6] Several studies have sought racial-ethnic differences in circulating androgen levels, with conflicting results. Ross et al[7] measured total testosterone levels in 50 African American and 50 Caucasian university students living in southern California, whose mean age was 20 years, and found a 19% higher total and a 21% higher free testosterone level in African Americans, whereas sex hormone-binding globulin (SHBG) binding capacity was not significantly different (5% higher in African Americans). Ettinger et al[8] found no significant difference in total (7.7% higher) or free (9.2% higher) testosterone or in SHBG (no difference) levels in young adult African American and Caucasian men, mean age 31 years, living in northern California. Wright et al[9] found a comparable total testosterone level (4.5% higher), but an elevated free testosterone index (46% higher), in 16 African American compared with 17 Caucasian men who ranged in age from 20 to 40 years and were living in South Carolina. Ellis and Nyborg[10] found slightly (3.3%) higher total testosterone levels in 525 African American compared with 3,654 Caucasian Army veterans from across the United States whose mean age was 38 years. No racial difference in testosterone concentration was found just prior to prostate biopsy in men with elevated prostate-specific antigen (PSA) levels, but no histologic evidence of prostate cancer,[11] or in men with clinically localized prostate adenocarcinoma.[12]

There is a diurnal variation in circulating testosterone concentrations in young adult men, with the highest values at 8 AM and the lowest values at 8 PM[13] with the average difference of about 20%. Because most of the above studies did not control for the effect of time of day on circulating testosterone levels, we measured testosterone and SHBG levels in the morning and evening and related these values to circulating insulin and waist circumference in young adult African American and Caucasian men.

MATERIALS AND METHODS

Subjects

Twenty-three African American and 23 Caucasian young adult men ages 18 to 24 years were recruited by advertisement from the undergraduate and graduate students at the University of Pittsburgh. Subjects with any active medical illness, history of gonadal dysfunction, daily use of alcohol, or status as elite athletes were excluded from the study. Informed consent was obtained according to a protocol approved by the Institutional Review Board for Biomedical Research. Subjects completed a questionnaire, were examined, and a blood sample was obtained at the General Clinical Research Center (GCRC) between 8:00 and 9:00 AM after an overnight fast. Testis size was measured with an orchidometer. A second blood sample was obtained the same day at 8:00 to 9:00 PM.

Assays

Total testosterone levels were measured with the Coat-A-Count total testosterone solid phase RIA kit (Diagnostic Products, Los Angeles, CA). The within-assay coefficient of variation (CV) was 1.1% at 3.5 ng/mL (12.3 nmol/L). SHBG was measured using the Active SHBG 2-site immunoradiometric assay kit (Diagnostic System Laboratories,

From the Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh; Department of Epidemiology, Graduate School of Public Health, the University of Pittsburgh Cancer Institute, Pittsburgh, PA; and the Division of Endocrinology and Metabolism, University of Louisville School of Medicine, Louisville, KY.

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Address reprint requests to Stephen J. Winters, MD, Division of Endocrinology and Metabolism, University of Louisville Health Sciences Center, ACB-A3G11, 530 S. Jackson St, Louisville, KY 40292.

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Webster, TX). The within-assay CV was 13.5% at 29 nmol/L and 9.7% at 107 nmol/L. The free testosterone concentration was calculated from the measured total testosterone and SHBG levels according to the law of mass action as described by Sodergard et al.[14] Association constants of SHBG and albumin for testosterone of 1×10^9 L/M and 3×10^4 L/M, respectively, were used for all samples. Total estradiol levels were measured with the Coat-A-Count estradiol assay kit (Diagnostic Products) with an intra-assay CV of 3.9% at 40 pg/mL (147 pmol/L). Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured with Nichols Allegro LH and FSH two-site immunoradiometric assays (San Juan Capistrano, CA). The within assay CVs were 4.7% and 5.0%, respectively. Insulin levels were measured using a radioimmunoassay kit from Linco Research (St. Charles, MO).

Data Analysis

Data are presented as mean ± SD. Mean hormone concentrations in African Americans and Caucasians were compared for significant differences using an independent samples *t* test. Circulating insulin levels were log transformed before analysis because the distribution of values was skewed. Scattergrams of SHBG were plotted by waist-to-hip ratio, and subsequent Pearson correlation coefficients were computed to assess any linear relationship between these variables. Linear least-square regression was used to estimate the effects of race on SHBG independent of insulin and waist-to-hip ratio. Influence diagnostics were computed for each of the regressions that were considered to be important. The diagnostics computed included Cook's D, which identifies outliers in both the outcome and predictors, the hat matrix, which identifies outliers in the predictors, and residuals, which identify outliers in the outcomes. In each case, the flagged observation was excluded from the model, and the model was refit to the smallest dataset.

RESULTS

Study Population

The clinical characteristics of the study population are summarized in Table 1. Although the study subjects ranged in age from 18 to 24 years, the mean age for Caucasians was 1.7 years older than for African Americans ($P < .001$). The 2 groups were similar in height, weight, and body mass index (BMI). On the other hand, the waist circumference ($P = .037$) and the waist-to-hip ratio ($P = .002$) were significantly higher in Caucasians than in African Americans. Five Caucasians and 5 Africans Americans were obese (BMI > 28 kg/m^2). The size of the testes was slightly smaller ($P < .05$) in African Americans than in Caucasians.

Table 1. Clinical Characteristics of the Study Population

	African Americans	Caucasians	*P* Value
Age (yr)	19.8 ± 1.4	21.5 ± 2.0	.001
Height (cm)	178 ± 7	178 ± 6	.77
Weight (kg)	79.6 ± 15.2	83.2 ± 15.2	.43
BMI (kg/m^2)	25.3 ± 4.9	25.7 ± 3.7	.64
Waist (cm)	80.7 ± 11.5	86.3 ± 9.13	.037
Waist-to-hip ratio	0.82 ± 0.04	0.87 ± 0.07	.002
Testis size (mL) L/R	24.9 ± 3.8/24.8 ± 3.7	27.5 ± 3.0/26.8 ± 3.1	.017/.048

NOTE. Values are mean ± SD (n = 23 per group).

Table 2. Serum Hormone Levels in Young Adult African American and Caucasian Men

	African Americans	Caucasians	*P* Value
Testosterone (ng/dL)	673 ± 131	538 ± 108	.0004
Free testosterone (pmol/L)	215 ± 56.1	208 ± 64.2	.70
SHBG (nmol/L)	107 ± 38.1	87.6 ± 26.7	.015
Estradiol (pg/mL)	47 ± 12	43 ± 9.2	.26
FSH (mIU/mL)	2.94 ± 1.66	3.12 ± 1.37	.69
LH (mIU/mL)	3.42 ± 1.92	3.03 ± 1.30	.43
Insulin (μU/mL)	16.4 ± 11.7	28.6 ± 36.0	.01

NOTE. Values represent the mean ± SD (n = 23 per group). For each subject, the mean of the morning and evening levels was determined, except for FSH and insulin, which represent the morning values. To convert testosterone and estradiol to SI units (nmol/L and pmol/L, respectively) multiply the value by 0.03467 and 3.671.

Circulating Hormone Concentrations

Serum levels of total testosterone, LH, and FSH were within the range of normal for all subjects. The average of the morning and evening hormone concentrations for each subject was computed, except for FSH, for which only morning values were available. As shown in Table 2, mean serum levels of total testosterone ($P = .0004$) and SHBG ($P = .015$) were significantly higher in the African American than in the Caucasian men, whereas free testosterone, estradiol, FSH, and LH levels were similar in the 2 groups.

Figure 1 illustrates the mean levels of total testosterone, SHBG, and free testosterone in African American and Caucasian men at 8:00 AM and 8:00 PM. A significant ($P < .001$) diurnal rhythm for total testosterone was found for both groups. Serum levels of total testosterone were 29.4% and 23.9% lower at 8:00 PM than at 8:00 AM in African American and Caucasian men, respectively. Total testosterone levels were significantly ($P < .01$) higher in African American than in Caucasian men in both the morning and evening specimens. SHBG levels were also higher ($P < .02$) in African Americans than in Caucasians at both times of day, but in neither group of men were SHBG values different at 8:00 AM compared with 8:00 PM. Free testosterone levels were similar in African American and Caucasian men at both 8:00 AM and 8:00 PM and were 30.3% and 28% lower ($P < .001$) in the evening than in the morning in both subject groups.

The scattergrams in Fig 2 show that the level of SHBG was higher as the waist-to-hip ratio decreased ($r = -.43$; $P < .025$) in African American men, but not in Caucasians. The level of SHBG in 4 of the 26 African American men exceeded the range of values observed (43 to 130 nmol/L) in the 26 Caucasians; each of these 4 men had a waist-to-hip ratio below 0.8.

We next sought to explore the role of insulin in the elevated SHBG concentrations in African American men. Fasting insulin levels were lower ($P < .01$) in African Americans than in Caucasians (16.4 ± 11.7 *v* 28.6 ± 36.0 μU/mL). In addition, the level of SHBG was inversely correlated with fasting insulin among African Americans (Fig 3) and for the group as a whole ($r = -.043$; $P < .05$). Regression analysis testing race, insulin, and waist-to-hip ratio as main effects and the interaction between race and waist-to-hip ratio was statistically significant

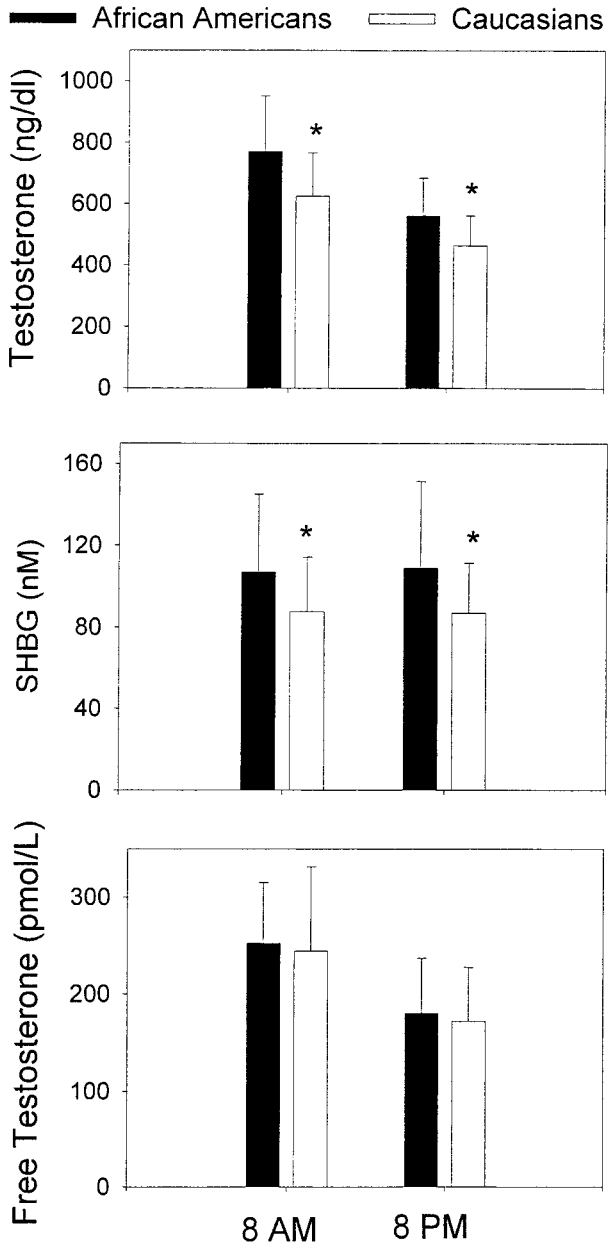

Fig 1. Diurnal variation in mean serum total testosterone, SHBG, and free testosterone levels in young adult African American and Caucasian men. *Significantly higher in African American than in Caucasian men in both the morning and evening specimens ($P < .01$ for total testosterone and $P < .02$ for SHBG). To convert testosterone to SI units (nmol/L), multiply the value by 0.03467.

($F = 3.968$, $P < .01$) and explained 29% of the variance in SHBG. The final analysis excluded 3 observations: 1 Caucasian missing waist-to-hip ratio, 1 Caucasian with an extreme insulin level of 180 μU/mL, and 1 Caucasian with a very low waist-to-hip ratio (0.723), low-insulin level (10.2 μU/mL), and high SHBG (130 nmol/L). Therefore, the final model included results from 23 African American and 20 Caucasian men. The coefficient for the race by waist-to-hip interaction indicated greater racial difference in SHBG at a lower waist-to-hip ratio. When adjusted for insulin and waist-to-hip ratio, SHBG was increased in African American relative to Caucasian men by an estimated 21.4 nmol/L.

DISCUSSION

Several studies[1-3,7-9,15] have sought to identify a role for androgens in the racial difference in prostate cancer risk and mortality that is highest in African Americans and lowest in native Chinese and Japanese men. In the current study, the first to examine the diurnal variation in serum testosterone levels characteristic of young adult men, the serum levels of SHBG and total testosterone were higher in African American than in Caucasian college students living in western Pennsylvania. The calculated free testosterone level was similar in both groups, however, implying a similar production rate for testosterone. Moreover, there was a comparable diurnal variation in total and free testosterone levels in African American and Caucasian men with mean levels 25% to 30% lower at 8:00 PM than at 8:00 AM. LH and FSH levels were similar in both groups, although FSH levels represented a single morning value for each subject.

SHBG is a circulating glycoprotein that is produced by the liver and binds testosterone and other steroids with high affinity[16] and is thereby an important predictor of the circulating total testosterone concentration in men.[17] Thus, it follows from

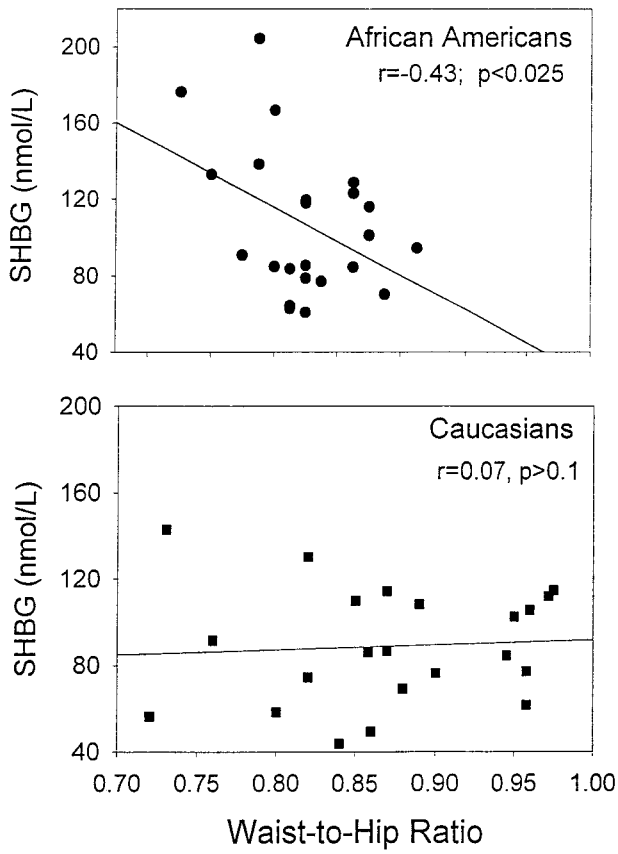

Fig 2. Correlation between the waist-to-hip ratio and circulating SHBG levels in African American and Caucasian men.

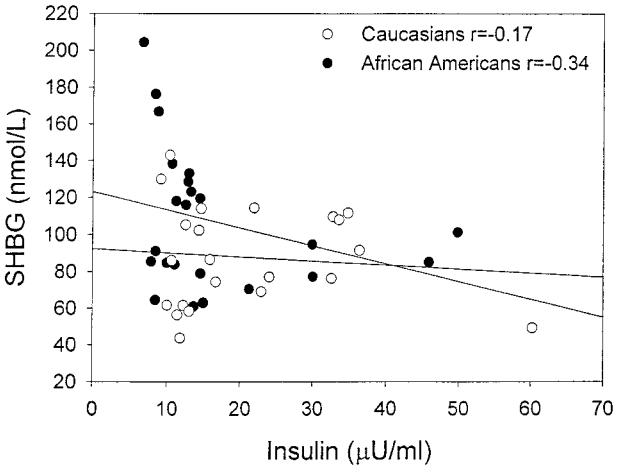

Fig 3. Relationship between fasting insulin levels and SHBG concentrations in African American and Caucasian men. The linear regression plot of the data for each group of subjects is presented. The results for 1 Caucasian with an extreme insulin level of 180 U/mL are omitted.

the higher level of SHBG that the total testosterone level was higher in African American men. Only slightly higher (not significant [NS]) levels of SHBG were reported in young adult African American than Caucasian men living in southern California,[1] and no racial difference in SHBG was found in young men living in northern California[8] or in South Carolina.[9] Possible reasons for these variable findings include small sample sizes, selection bias, differences in laboratory methodology, changes in population characteristics over calendar time, and nonhomogeneity of African American-Caucasian differences with respect to geographic place of residence, perhaps related to exercise and dietary habits.

The higher SHBG levels in African American men in the present study appear to be partly on an environmental/metabolic basis in that their waist circumference and waist-to-hip ratio was less, and circulating insulin levels were lower than in Caucasians. Diet and exercise are important determinants of both intra-abdominal fat[18] and SHBG[19,20] and may have differed in our study groups, but these factors were not formally evaluated. Many studies have shown that SHBG levels are reduced in obese men,[21-23] and some,[23] but not all[24,25] studies have found an inverse relationship between visceral fat and SHBG in men. Although visceral fat was not measured in our study, the waist-to-hip ratio, a predictor of visceral fat, was lower in the young adult African American men. Likewise, African American men living in Birmingham, AL and Oakland, CA, who were participating in the CARDIA (Coronary Artery Risk Development in Young Adults) study, were reported to have a reduced waist-to-hip ratio and less visceral fat for a given body fatness compared with Caucasians.[26] Moreover, the waist circumference was lower in middle-aged African American than in Caucasian men in the Third US National Health and Nutrition Examination Survey (NHANES III).[27]

Circulating SHBG levels are regulated by multiple hormonal factors (reviewed in Joseph,[16], Selby,[28], and Haffner[29]). SHBG is downregulated by insulin, insulin-like growth factor (IGF)-1, glucocorticoids, and testosterone and is upregulated by thyroxine and estradiol. Increased visceral fat is known to predict insulin insensitivity[30] and hyperinsulinemia,[20] and insulin inhibits SHBG production in vitro.[31] Therefore, higher levels of SHBG would be expected from the lower insulin levels of African American men, as shown previously in other populations.[32] Other factors may, however, contribute to the elevated SHBG levels in African American men in that SHBG levels remained elevated when adjusted for fasting insulin concentrations. These additional factors may explain the finding of an inverse correlation between SHBG and waist-to-hip ratio in African American, but not in Caucasian men.

No difference in circulating estradiol levels was found between African Americans and Caucasians. Therefore, elevated estradiol levels cannot account for the observed increase in SHBG, although higher plasma estradiol levels were reported in adolescent and young adult African American and Caucasian males.[9,33] In 1 study,[9] IGF-1 levels were higher in African American men, a change that would tend to decrease, rather than increase, SHBG concentrations. Finally, there are no established racial differences in free cortisol excretion or plasma cortisol levels[34] or in thyroid hormone concentations[35] in men, which are also determinants of plasma SHBG, but were not measured in this study.

SHBG, a dimer, is coded for by a normal and at least 1 variant allele that is localized to the p12-p13 bands of chromosome 17.[36] The frequency of the variant allele was lowest in samples from Zaire (0.03), intermediate in Caucasians from Belgium, (0.135) and highest in samples from China (0.152), a relationship that is consistent with racial prostate cancer risk. The mutation creates an additional site for N-linked glycosylation of the mature protein, which is therefore cleared more slowly from the circulation than is the wild-type.[37] Therefore, high SHBG in African American men could have, in part, a genetic basis, although the mutation is uncommon. The binding affinity of the wild-type and the variant protein for dihydrotestosterone (DHT) were comparable, and no data on DHT binding capacity were reported.[36]

Whether there is a link between elevated SHBG and total testosterone in young adulthood and prostate cancer risk among African American men as they grow older is uncertain. Interestingly, total testosterone and SHBG levels in young adult ethnic Chinese men living in China, among whom prostate cancer is uncommon, were reported to be slightly lower than in Caucasians.[15] Although the results from the Physicians Health Study[2] of middle-aged, mostly Caucasian men indicated that high levels of circulating testosterone, when combined with low levels of SHBG, were associated with an increased relative risk of prostate cancer, a second study of middle-aged men from Finland[38] found no link between SHBG and the subsequent occurrence of prostate carcinoma.

SHBG is generally considered as a transport protein for testosterone and other steroids. However, specific binding sites for SHBG have been described on prostate cell membranes,[39] and estradiol and 5α-androstan-3α-17β diol (3α diol) when added together with SHBG stimulate cyclic adenosine monophosphate (cAMP) production by human prostate.[40] There is recent evidence that androgen receptors (AR) can be activated by nonsteroidal agents, such as growth factors, or by elevation

of cAMP.[41] For example, 8-Br-cAMP increased several-fold the effect of androgens to activate several androgen-induced genes,[42] and forskolin was found to stimulate the PSA promoter through an AR-dependent mechanism.[43] Moreover, cAMP stimulates transcription of the AR gene.[44] Accordingly, it is intriguing to propose that increased SHBG in some young adult African American men increases responsiveness of prostate epithelium to androgen, and thereby stimulates cell division, allowing for the expression of oncogenes, which facilitate the carcinogenic process as men grow older. The finding that the range of values for plasma PSA is higher among older African American men[45,46] could reflect this lifelong increased activation of prostatic epithelium.

In summary, among male college students in western Pennsylvania, SHBG and total testosterone concentrations are increased in African Americans compared with Caucasians in both the morning and evening hours. Elevated SHBG levels in young adult African American men are associated with a lower waist circumference and waist-to-hip ratio and a lower circulating insulin concentration. From these findings, we propose that SHBG is elevated in young adult African American men on an endocrine-metabolic basis. Further, we hypothesize that higher SHBG in young adulthood may contribute to the increased risk of prostate cancer among African American men as they grow older through cAMP-dependent protein kinase A activation of androgen responsive genes.

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