Serum Androgen Concentrations in Young Men: A Longitudinal Analysis of Associations with Age, Obesity, and Race. The CARDIA Male Hormone Study[1]

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Abstract

Serum testosterone concentration appears to be higher in black men than white men, particularly at younger ages. The higher incidence of prostate cancer in blacks has been attributed, at least in part, to this difference. Other factors associated with androgen levels in men include age and obesity. However, most of the studies of adult androgen levels are limited by their cross-sectional design. We conducted longitudinal analyses (Generalized Estimating Equation) of the associations of age, body mass index (BMI), and waist circumference with total and free testosterone and sex hormone-binding globulin (SHBG) concentrations during an 8-year period and compared these hormonal factors between black ($n = 483$) and white ($n = 695$) male participants of the Coronary Artery Risk Development in Young Adults (CARDIA) Study. For men ages 24 years and older at the time of the first hormone measurement, increasing age was associated with a statistically significant decrease in serum total and free testosterone and an increase in SHBG ($P < 0.05$). BMI and waist circumference were inversely associated with total testosterone and SHBG, but only BMI was inversely associated with free testosterone. After adjustment for age and BMI, total testosterone was higher in blacks (0.21 ng/ml; $P = 0.028$) than whites, an approximately 3% difference. However, after further adjustment for waist circumference, there was no black-white difference (0.05 ng/ml; $P = 0.62$). These results indicate that the age-associated decrease in circulating testosterone and increase in SHBG begin during the 3rd decade of life, and that increasing obesity, particularly central obesity, is associated with decreasing total testosterone and SHBG. Results also suggest that the previously observed difference in total testosterone between black and white men could be attributed, for the most part, to racial differences in abdominal obesity.

Introduction

Among men living in the United States, prostate cancer is the most commonly occurring non-skin cancer and the second most common cause of cancer mortality (1). However, across all age groups, incidence and mortality rates are considerably higher among blacks compared with whites. Investigators have proposed (2) that differences in testosterone levels between black and white men could account, at least in part, for the disparate rates of prostate cancer between these two populations. Some studies have reported higher concentrations of total testosterone in black men compared with white men (2–5). Results of one of these studies (3) suggest that the black-white difference in testosterone is reduced in older- compared with younger-age groups.

Other potentially important determinants of sex hormone concentrations in men include age and obesity. Indeed, serum total and free testosterone concentrations appear to decrease with age, and SHBG[3] appears to increase with age (6, 7). However, the age at which these changes begin to occur is unclear. Cross-sectional epidemiological studies have shown inverse relationships of overall obesity (*e.g.*, BMI), and central obesity (*i.e.*, waist:hip ratio) with circulating levels of testosterone, and SHBG (4, 7–10).

In previous longitudinal studies of androgen profiles in men, the average age at baseline was greater than 50 years and the study samples were predominantly white (11–13). A longitudinal analysis of serum hormonal factors in young black and white men is particularly important because of the possibility that the black-white differences in androgen levels change with aging and because levels in young adulthood could affect the early pathogenesis of diseases with long latency periods, such as prostate cancer. Moreover, because the level of obesity differs among ethnic/racial groups (14, 15) and obesity frequently changes with age (15), measures of body size must be carefully considered in studies of ethnic/racial comparisons in hormonal factors.

The CARDIA study is a longitudinal study of young black and white men and women. This cohort provides a unique

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[3] The abbreviations used are: SHBG, sex hormone-binding globulin; BMI, body mass index; CARDIA, Coronary Artery Risk Development In (Young) Adults (study); CMHS, CARDIA Male Hormone Study.

opportunity for disentangling the associations of age, obesity, and race with hormone levels. The large size of the cohort allows for the detection of small differences in hormone levels between black and white men that could be important biologically, because these differences may act cumulatively over many years. In addition, repeat measurements of body size and blood sampling provide a basis for examining longitudinal changes in serum androgen levels beginning during young adulthood, when many lifestyle changes are occurring. The CMHS was designed to compare 8-year changes in serum hormone levels between black and white male CARDIA participants. In this longitudinal analysis, we compared serum total and free testosterone and SHBG concentrations between black and white men. We also examined the relationships of age and measures of overall obesity (BMI), as well as central obesity (waist circumference; Refs. 16, 17) with androgen and SHBG levels, and on black-white differences in particular.

Materials and Methods

The CARDIA Male Hormone Study. The CARDIA Study is a multicenter, longitudinal study designed to examine physiological, psychological, and lifestyle factors that might affect the development of cardiovascular disease risk factors in young, black and white, men and women. Briefly, 5115 participants, ages 18–30 years, completed a baseline examination in 1985–1986 at one of four clinical centers: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota, or Oakland, California. Four follow-up examinations were completed in 1987–1988 (Year 2), 1990–1991 (Year 5), 1992–1993 (Year 7), and 1995–1996 (Year 10). A detailed description of the design, recruitment, and methods of this study was published previously (18).

The number of black and white men who completed the baseline examination was 1157 and 1171, respectively. It is important to note that within each clinical center, the proportion of black and white men screened was similar. For the CMHS, hormone concentrations were measured in serum collected at the Year 2, Year 7 (when available), and Year 10 examinations. Because the primary goal of this study was to evaluate 8-year longitudinal changes in hormone levels, only men who had serum available from both the Year 2 and the Year 10 examinations were included, *i.e.,* 624 black men and 796 white men. Among these 1420 men, 2 (black men) were excluded because their baseline age was more than 31 years. Within each race group, there were no statistically significant differences in baseline BMI or waist:hip ratio between those men for whom hormones were and were not measured. For white men, baseline age and education did not differ. However, black men included in the study were slightly older than those not included (24.4 *versus* 23.9 years, respectively: $P = 0.03$), and had slightly more years of education (13.1 *versus* 12.7; $P = 0.0002$). The CMHS has been approved by the institutional review board at Northwestern University.

Data Collection. In the CARDIA study, all of the data collection technicians were centrally trained and certified. The CARDIA Coordinating Center and the CARDIA Quality Control Committee monitored data collection throughout the study. Informed consent was obtained from each participant at each examination.

Participants were asked to fast for 12 h and to avoid smoking and heavy physical activity for 2 h before each examination. Weight and height were measured using a balance beam and a vertical ruler with participants wearing light clothing and no shoes. Height was recorded to the nearest 0.5 cm and weight to the nearest 0.5 pound. BMI was calculated as the weight (kg) divided by the height squared (m^2). Waist circumference was measured in duplicate at the minimum abdominal girth; age, race, and years of education were self-reported. Other self-reported information included the use of prescription medication. A subset of medications may influence levels of steroid hormones or steroid-binding proteins and/or interfere with hormone binding. Therefore, medications were classified into the two categories: (*a*) regulation or interference with binding likely and (*b*) regulation or interference with binding unlikely/possible.

At each of the three examinations, blood was collected by venipuncture between 7:30 a.m. and 12 noon from >95% of the CMHS participants, and there were no meaningful differences in average time of blood draw between black and white men. Aliquots of serum were transferred to appropriately labeled tubes and immediately stored at −70°C. Samples were packed in dry ice and shipped to a long-term freezer storage facility at Solomon Park Research Laboratories, in Kirkland, WA. The samples used in this study had not been thawed previously.

Hormone Measurements. Total testosterone was measured directly using RIA kits, and SHBG was measured by chemiluminescent enzyme immunometric assay using Immulite obtained from Diagnostic Products Corporation (Los Angeles, CA). Percentage of free testosterone was calculated according to the method of Södergard *et al.* (19, 20), and free testosterone concentrations were calculated as (total testosterone) × (percentage free testosterone × 0.01). Assay variability was monitored by including ~10% blind, quality control samples in each batch of samples analyzed. The quality control serum was obtained from a large pool that was aliquoted into storage vials and labeled identically to CARDIA participant samples. The intra- and interassay technical errors were 12.3 and 11.2%, respectively, for total testosterone; 7.9 and 11.2%, respectively, for SHBG; and 5.9, and 7.4%, respectively, for free testosterone. The age and BMI-adjusted partial correlations between time of blood draw and all hormone levels were ≤0.09. Thus, the relationships between time of blood draw and hormone levels were not considered further.

Statistical Analysis. Serum concentrations of total testosterone, SHBG, and free testosterone appeared normally distributed for both black and white men. Race-specific mean hormone levels for each 2-year age group at the Year 2 examination were graphed to examine the general associations of hormone levels with age. For total testosterone, the graphs were suggestive of two separate age-trends for men less than age 24 years *versus* men ages 24 years and older. Therefore, race-specific linear regression analysis was conducted to compare the slopes of the two age-trends as described by Draper and Smith (21). The models incorporated two dummy variables for age where $D1 = 1$, 2, or 3 for ages 20, 21, and 22 years, respectively, and $D1 = 4$ for ages 23 years and older; $D2 = 0$ for ages 20 through 23 years, and $D2 = 1, 2, 3 \ldots 11$ for ages 24–34 years. The equality of the corresponding regression coefficients was tested. Results suggested opposing slopes between the two age groups. Therefore, men under age 24 were excluded in longitudinal analyses because of the difference in the relationship of age with total testosterone concentration between younger and older men. However, cross-sectional analyses of the Year 2 hormone concentrations were conducted for men ages 20–23 years using multivariate linear regression to assess black-white differences in total testosterone adjusted for age, and further adjusted for BMI and waist circumference.

Student's *t* tests were used to compare racial differences in

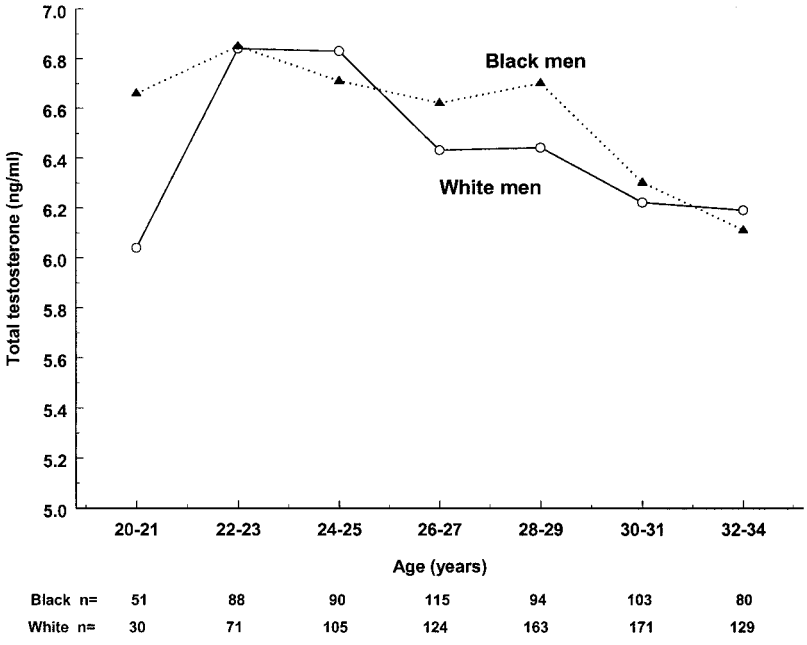

Fig. 1. Mean concentration of total testosterone for 2-year age groups in serum samples obtained at the Year 2 CARDIA examination for black men (▲) and for white (○) men. The total number of black and white men may not total 624 and 796, respectively, because of missing data.

BMI and waist circumference measurements for each examination and for the 8-year change in these anthropometric measures for men ages 24–34 years at the Year 2 examination. For each hormone, Spearman rank correlation coefficients between concentrations measured at the Years 2 and 7, and the Years 2 and 10 exams were computed.

The primary analysis was based on the Generalized Estimating Equation method developed by Liang and Zeger (22). This method allows for simultaneously examining the cross-sectional relationships between each of the independent variables and hormone levels, and the relationships between changes in these variables and changes in hormone levels. A typical model for this study is:

$$Y_{it} = \beta_0 + \beta_1 T_7 + \beta_2 T_{10} + \beta_3 U_{it} + \beta_4 X_i + \beta_5 Z_{i2} + \beta_6 \Delta Z_{it} + e_{it}$$

where for $t = 2$, 7, or 10, Y_{it} is the hormone concentration for person i at year t; T_7 and T_{10} are indicator variables where T_7 indicates the Year 7 exam, and T_{10} indicates the Year 10 exam, U_{it} is the age of person i at time t; X_i = is the dummy variable to separate the two race groups; Z_{i2} is the Year 2 exam value of a covariate (*i.e.*, BMI or waist circumference); $\Delta Z_{it} = Z_{it} - Z_{i2}$, is the change in BMI or waist circumference between the Year t and Year 2 exams for person i), and e_{it} is the error term.

The coefficients β_1 and β_2 measure the secular change in hormone level between the Years 2 and 7 or -10 exams, respectively, that is not related to changes in age or the other covariates. The coefficient β_3 measures the covariate-adjusted association between hormone level and visit age. The coefficient β_4 measures the average difference in hormone level between black and white men. The coefficient β_5 measures the relationship between average hormone concentration and Year 2 BMI (or waist circumference) adjusting for covariates, whereas β_6 measures the association of changes in BMI (or waist circumference) and changes in hormone levels over time. A cross-product term for race and visit age was also included to determine whether the relationship of race with hormone or SHBG level differed according to age. Additionally, the inclusion of a time-dependent indicator variable for medications that were categorized as "likely" to regulate or interfere with binding of androgens did not change the associations of hormones with race, age, or measures of obesity. Therefore, results are presented without adjustment for medication use. All of the analyses were conducted using SAS version 8.0 (SAS Institute Inc., Cary, NC). For the longitudinal analyses, PROC GENMOD was used, and an exchangeable structure was specified for the within-subject correlation.

Results

Preliminary Analyses. Race-specific mean concentrations of total testosterone for each 2-year age group in the Year 2 serum samples are shown in Fig. 1. For both blacks and whites, total testosterone was higher in men ages 22–23 years, compared with men 20–21 years old, whereas after age 24, testosterone concentrations appeared to decrease. In linear regression analysis, the regression coefficients relating age to total testosterone concentration for black men ages 20–23 years and men ages 24 years and older were $\beta_{20-23} = 0.05$ ng/ml and $\beta_{>24} = -0.06$ ng/ml, respectively ($P = 0.47$). For white men, the comparable regression coefficients were $\beta_{20-23} = 0.35$ ng/ml and $\beta_{>24} = -0.08$ ng/ml, respectively ($P = 0.01$). In multivariate regression analysis of men 20–23 years at the Year 2, there was no black-white difference ($P > 0.25$) in serum total testosterone concentration with or without adjustment for age or BMI (and additionally waist circumference). As mentioned previously, because of the difference in the relationship of age with testosterone concentration between younger and older men, we excluded the 141 black men and 101 white men who were ages 20–23 years from all of the subsequent analyses and included only the 483 black men and 695 white men who were ages 24 years and older.

Univariate Comparisons between Black and White Men. Among men ages 24 years and older at the Year 2 CARDIA examination, the average ages of black and white men were 28.4 and 28.8 years, respectively ($P = 0.009$). Unadjusted mean total testosterone, SHBG, and free-testosterone concen-

Table 1 Unadjusted race-specific means (SD) for hormonal factors and selected anthropometric measures at the years 2, 7, and 10 examinations in black ($n = 483$) and white ($n = 695$) mean ages 24–34 years at the year 2 CARDIA examination

Variable	Exam year	Black men			White men			P for difference
		n^a	Mean	(SD)	n^a	Mean	(SD)	
Total testosterone (ng/ml)	2	482	6.5	(2.0)	692	6.40	(2.00)	0.40
	7	397	5.8	(1.7)	614	5.75	(1.80)	0.57
	10	483	5.8	(2.0)	695	5.69	(1.80)	0.36
	10−2	482	−0.7	(1.9)	692	−0.71	(1.70)	0.98
SHBG (nmol/liter)	2	481	31.7	(12.8)	692	31.40	(12.63)	0.72
	7	397	30.1	(13.6)	614	30.45	(13.31)	0.71
	10	483	29.2	(13.4)	695	29.95	(13.55)	0.34
	10−2	481	−2.46	(11.4)	692	−1.45	(10.44)	0.12
Free testosterone (ng/ml)	2	481	0.17	(0.06)	692	0.17	(0.06)	0.34
	7	397	0.16	(0.05)	614	0.15	(0.05)	0.18
	10	483	0.16	(0.06)	695	0.15	(0.05)	0.05
	10−2	481	−0.02	(0.06)	692	−0.02	(0.06)	0.42
BMI (kg/m^2)	2	477	25.8	(4.7)	695	25.0	(3.7)	0.006
	7	393	27.4	(5.3)	614	26.1	(4.2)	<0.0001
	10	480	27.9	(5.5)	695	26.7	(4.4)	<0.0001
	10−2	474	2.1	(2.6)	695	1.6	(2.2)	0.001
Waist circumference (cm)	2	480	84.2	(11.0)	694	85.6	(9.4)	0.03
	7	396	88.9	(12.6)	612	88.7	(10.7)	0.79
	10	479	90.8	(13.6)	692	90.6	(11.2)	0.75
	10−2	476	6.7	(7.2)	691	5.2	(6.1)	0.0002

[a] Because of missing data, the total number of black and white men may be less than 483 and 695, respectively.

Table 2 Association of total testosterone with age, ethnicity, BMI, and waist circumference; regression coefficients (β)[a] from Generalized Estimating Equations

Variable	Model 1[b]		Model 2[b]		Model 3[b]	
	β (ng/ml)	P	β (ng/ml)	P	β (ng/ml)	P
Visit age, per yr	−0.0579	0.0013	−0.0521	0.0024	−0.0433	0.012
Black race	0.0764	0.44	0.2059	0.028	0.0493	0.62
Year 2 BMI, per 1 kg/m^2			−0.1091	<0.0001	0.0119	0.65
Δ BMI, per 1 kg/m^2			−0.1766	<0.0001	−0.1087	<0.0001
Year 2 waist circumference, per 1 cm					−0.0544	<0.0001
Δ waist circumference, per 1 cm					−0.0278	0.0006

[a] Mean change in total testosterone corresponding to the indicated difference in the independent variable.
[b] Each of the models also included terms for secular changes in hormone levels between the Years 2 and 7, and the Years 2 and 10 examinations.

trations were not statistically significantly different between blacks and whites at any examination (Table 1), except at Year 10, blacks had slightly higher levels (0.0063 ng/ml; $P = 0.05$) of free testosterone than whites. From the Year 2 to the Year 10 examinations, the concentrations of total and free testosterone were reduced by a similar magnitude for both black and white men. Although the reduction in SHBG was greater in black men compared with white men, this difference was not statistically significant.

At each examination, the mean BMI was significantly higher in black men than white men, and the increase from Year 2 to Year 10 was 0.5 kg/m^2 greater in blacks than in whites (Table 1). Although average waist circumference was 1.4 cm lower in blacks than in whites at the Year 2 examination, there were no meaningful black-white difference in waist circumference at the Year 7 or 10 examinations. Thus, the 8-year change in waist circumference was significantly greater, ~1.5 cm, for black than for white men.

We also computed Spearman rank correlations between the Years 2 and 7 and Year 2 and 10 examinations for each hormone. For total testosterone, the correlations between the Year 2 and 7 concentrations were 0.58 for black men and 0.64 for white men, and between the Years 2 and 10 concentrations were 0.57 and 0.61 for black and white men, respectively. For SHBG, the correlations between Years 2 and 7 were 0.73 for black and 0.76 for white men, and between Years 2 and 10 were 0.68 and 0.71 for black and white men, respectively. For free testosterone, the correlations between Years 2 and 7 were 0.49 for black and 0.49 for white men, and between Years 2 and 10 were 0.48 and 0.50 for black and white men, respectively.

Associations of Age, Race, and Measures of Obesity with Total Testosterone. Table 2 shows the regression coefficients from three longitudinal analysis models for total testosterone. Age was inversely associated with change in serum total testosterone concentration in all three of the models. In Model 2, Year 2 BMI and 8-year change in BMI were significantly inversely related with total testosterone concentration, although the longitudinal decrease in testosterone associated with an 8-year increase in BMI was greater than the cross-sectional association. In Model 3, Year 2 waist circumference and change in waist circumference were also included to determine the relationship of central adiposity, beyond that associated with overall adiposity (*i.e.*, BMI), with total testosterone. There were strong inverse cross-sectional and longitudinal relationships of waist circumference with serum testosterone levels. Notably, inclusion of waist circumference attenuated the cross-sectional relation of BMI with testosterone by nearly 90%.

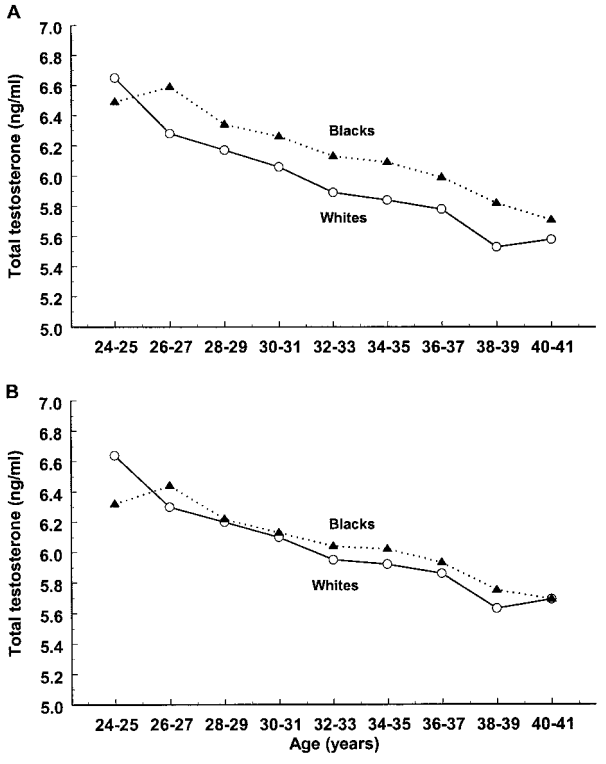

Fig. 2. Age-associated change in total testosterone over an 8-year period for black men (▲) and for white (○) men after adjustment for BMI (*A*), and after adjustment for BMI and waist circumference (*B*).

There was no significant difference in the testosterone level between black and white men after the adjustment for age. As seen in Model 2, further adjustment for Year 2 BMI and change in BMI resulted in a significantly higher (*i.e.*, ~0.21-ng/ml) concentration of testosterone in blacks than in whites. However, in Model 3, after inclusion of Year 2 waist circumference and change in waist circumference, there was no black-white difference in total testosterone. In addition, as indicated by the slopes of the curves in Fig. 2, the age-associated change in testosterone was similar between black and white men after adjustment for waist circumference and/or BMI.

Associations of Age, Race, and Measures of Obesity with SHBG. Increasing age was independently associated with increasing SHBG (Table 3). Conversely, in Model 2, serum SHBG was inversely related to Year 2 BMI and change in BMI. Comparing Models 2 and 3, the Year 2 cross-sectional relationship between BMI and SHBG was reduced after the inclusion of waist circumference, but there was only a marginal reduction in the magnitude of the regression coefficient for change in BMI associated with change in SHBG level. In addition, the cross-sectional association of waist circumference with SHBG was much stronger than the association between change in waist circumference and change in SHBG concentration. Overall, there were no meaningful differences in serum SHBG concentration between black and white men in any model.

Associations of Age, Race, and Measures of Obesity with Free Testosterone. Similar to total testosterone, age also was inversely related to free testosterone in all of the models (Table 4). In Model 2, there were statistically significant inverse associations of Year 2 BMI and change in BMI with free testosterone. Similarly, there was a weak inverse association of Year 2 waist circumference with free testosterone, but no meaningful association between change in waist circumference and change in free-testosterone concentration. Moreover, the concentration of free testosterone did not differ between black and white men after adjustment for all of the covariates.

Discussion

It is well recognized that androgens play an important role in regulating the normal proliferation and differentiation of prostate cells, as well as in the development and progression of prostate cancer (23–25). Although the variables associated with endogenous sex hormone concentrations in men are not completely understood, results of previous studies suggest that age, obesity, and black race are three potentially important factors. The primary objectives of this study were to determine the independent associations of changes in age, BMI, and waist circumference with changes in serum total and free testosterone, and in SHBG concentrations over an 8-year period, and to examine whether these hormonal factors differed between young black and white men.

In males, androgen secretion increases during puberty, and decreases during adulthood (26). In a large cross-sectional study of men ages 39–70 years, serum total testosterone, albumin-bound testosterone, and free testosterone levels decreased by 0.4, 1, and 1.2% per year, respectively, whereas SHBG increased by 1.2% per year (7). Similar findings were reported in longitudinal studies of men whose average was 50 years or older at the time of the first hormone measurement (11, 12). As mentioned previously, the age at which androgen levels begin to decline is not well established. In a cross-sectional analysis of our data, total testosterone appeared to increase from age 20 to 23 years. However, this finding should be interpreted with caution because of the narrow age-range considered. In the longitudinal analysis of men ages 24–34 years at the initial hormone measurement, increasing age was independently associated with decreases in total and free testosterone and with an increase in SHBG. Thus, this study provides strong evidence that the decline in serum testosterone and the increase in SHBG concentrations begins during the 3rd decade of life.

Another important determinant of endogenous hormonal factors is obesity, although this relationship is complex, and the nature of this relationship is not firmly established. In men, inverse associations between weight, BMI or waist:hip ratio and circulating levels of testosterone (*i.e.*, total, free, and/or bioavailable), SHBG and other androgens were reported from several cross-sectional epidemiological studies (4, 7, 8, 10, 27). Among 157 men enrolled in the Multiple Risk Factor Intervention Trial, a 1-year weight gain was inversely associated with plasma total testosterone level (28). Consistent with these findings, in our longitudinal study, increases in BMI were consistently associated with declines in serum total and free testosterone, and with SHBG concentrations. Similarly, there was an independent association of increasing waist circumference with lower total testosterone and SHBG concentrations, although only the cross-sectional association of waist circumference with SHBG was statistically significant. The effect of waist circumference on these hormonal factors, beyond its contribution to overall obesity, could be caused, in part, by the strong association of abdominal obesity with insulin production and/or insulin resistance. High abdominal obesity is associated with increasing insulin levels in circulation (29). *In vitro*, insulin inhibits SHBG production by hepatoma cells (30). Circulating

Table 3 Association of SHBG with age, ethnicity, BMI, and waist circumference; regression coefficients (β)[a] from Generalized Estimating Equations

Variable	Model 1[b]		Model 2[b]		Model 3[b]	
	β (nmol/liter)	*P*	β (nmol/liter)	*P*	β (nmol/liter)	*P*
Visit age, per yr	0.3103	0.011	0.3775	0.0011	0.4364	0.0002
Black race	−0.0864	0.90	0.8727	0.19	−0.1655	0.81
Year 2 BMI, per 1 kg/m^2			−0.9082	<0.0001	−0.1452	0.41
Δ BMI, per 1 kg/m^2			−1.4084	<0.0001	−1.1407	<0.0001
Year 2 waist circumference, per 1 cm					−0.3567	<0.0001
Δ Waist circumference, per 1 cm					−0.1091	0.17

[a] Mean change in SHBG corresponding to the indicated difference in the independent variable.
[b] Each of the models also included terms for secular changes in hormone levels between the Years 2 and 7, and the Years 2 and 10 examinations.

Table 4 Association of free testosterone with age, ethnicity, BMI, and waist circumference; regression coefficients (β)[a] from Generalized Estimating Equations

Variable	Model 1[b]		Model 2[b]		Model 3[b]	
	β (ng/ml)	*P*	β (ng/ml)	*P*	β (ng/ml)	*P*
Visit age, per yr	−0.0030	<0.0001	−0.0030	<0.0001	−0.0029	<0.0001
Black race	0.0035	0.18	0.0049	0.068	0.0033	0.23
Year 2 BMI, per 1 kg/m^2			−0.0008	0.014	0.0005	0.47
Δ BMI, per 1 kg/m^2			−0.0016	0.0046	−0.001	0.19
Year 2 waist circumference, per 1 cm					−0.0005	0.063
Δ Waist circumference, per 1 cm					−0.0002	0.32

[a] Mean change in free testosterone corresponding to the indicated difference in the independent variable.
[b] Each of the models also included terms for secular changes in hormone levels between the Year 2 and 7, and the Years 2 and 10 examinations.

SHBG concentration is inversely associated with insulin level (8, 31) and positively associated with insulin sensitivity (32). Lower SHBG concentrations could in turn reduce overall testosterone secretion as a result of the androgen-mediated feedback mechanisms on the hypothalamic-pituitary-gonadal axis.

Besides age and obesity, ethnicity/race also appears to be a potential determinant of circulating androgen levels. In a cross-sectional study of 100 college age men, Ross *et al.* (2) reported that serum total and free testosterone concentrations were 15 and 13% higher, respectively, in blacks compared with whites after adjusting for age, weight, and lifestyle factors; there was no black-white difference in serum SHBG concentration. In a subsequent study of male veterans ages 31–50 years (3), age- and weight-adjusted total testosterone levels were 3.3% higher ($P = 0.016$) in blacks compared with non-Hispanic whites. This difference was age dependent; for black men ages 31–34, 35–39, and 40–50 years, serum testosterone was 6.6, 3.7, and 0.5% higher, respectively, than for white men of comparable ages. In two other cross-sectional studies of men ages 47 years or 60 years and older, respectively, blacks had higher testosterone concentrations than whites, but these differences were not statistically significant (4, 5). Overall, the results of these studies suggest that younger black men have higher androgen levels than white men, but that these differences diminish with aging.

The findings presented here argue against any significant difference in androgen levels between black and white men after taking into account BMI and waist circumference. Indeed, the inclusion of waist circumference as a potential confounding factor in the associations of race with hormone levels provides a plausible explanation for differences in the results of this study with that of previous studies (2–5). One of the previous studies adjusted only for age (5), whereas others also considered weight or BMI in their analysis (2–4), but not a measure of central adiposity. Moreover, our data do not support a black-white difference in the age-related declines in serum testosterone.

One of the primary strengths of the present study is the availability of data from a large number of young adult black and white men for whom multiple blood samples were collected over an 8-year period. In addition, utilization of a standardized protocol for serial measurement of anthropometric factors reduces the degree of measurement error. One of the potential limitations is the relatively low ability of a single blood draw at each examination to characterize an individual's hormonal status because of diurnal variation in serum testosterone concentrations. However, it is unlikely that variation in time of blood draw had a marked effect on the results because venipuncture was performed in nearly all of the men between 7:30 a.m. and 12 noon, and the correlation between time of blood draw and each hormonal factor was negligible. Finally, the small volume of serum available (~0.5 ml) precluded the measurement of other hormonal factors that affect endogenous steroid hormone production (*e.g.*, luteinizing hormone), or androgen metabolism (*e.g.*, dihydrotestosterone).

In conclusion, the results of this longitudinal study of black and white men demonstrate that the age-associated decrease in circulating testosterone and increase in SHBG begin during the 3rd decade of life. However, for each hormone, the fairly high Spearman correlations between each two exams indicates that the measurement of a single hormone measurement at one time could reflect the relative ranking of individuals over time. Therefore, the cumulative exposure to testosterone may be greater among men whose testosterone levels are higher at younger ages because hormone levels may track over time. In addition, overall and central obesity, in particular, are independently and inversely associated with serum total testosterone and SHBG. It is conceivable that central obesity, a potentially modifiable factor, is partially contributing to the pathogenesis of hormonally related cancers, such as prostate cancer, by modulating endogenous hormonal factors, in particular, SHBG. Challenging the concept of differences in testosterone levels between black and white men, our results also indicate no differences in serum testosterone or SHBG concen-

trations after adjustment for age, BMI, and waist circumference. Thus, it is unlikely that circulating androgen levels explain the black-white difference in prostate cancer incidence. However, these results do not preclude the possibility of black-white differences in intracellular androgen levels, and/or androgen action that could result from variations in genetic factors associated with hormone metabolism.

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