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Associations of androgens with physical activity and fitness in young black and white men: the CARDIA Male Hormone Study

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Abstract

Objective—The association between physical activity or cardiovascular fitness and chronic disease risk in men might be mediated, in part, through androgens. Limited data exists on the potential associations of activity or fitness with serum hormones. We examined the associations of serum testosterone and sex hormone binding globulin (SHBG) concentrations with physical activity and cardiorespiratory fitness in black and white young men.

Method—Data were collected from 391 black and 604 white male participants of the Coronary Artery Risk Development in (Young) Adults (CARDIA) Male Hormone Study aged 24–32 in 1992–1993. Cross-sectional associations of serum total testosterone (TT), bioavailable testosterone (BT) and SHBG levels with self-reported total physical activity score, and in a subset of men (n=617) with cardiorespiratory fitness measured via duration on a treadmill test were assessed. Five-year longitudinal associations of change in hormones with changes in physical activity also were examined.

Results—There were no cross-sectional or longitudinal associations of physical activity with SHBG, TT or BT in either black or white men. Fitness was positively associated with SHBG only in white men, but was not associated with TT or BT in either group.

Conclusion—Overall the results do not support an association of self-reported physical activity with androgens, whereas they do suggest that fitness might be associated with SHBG in white men.

Keywords

testosterone; physical activity; cardiorespiratory fitness; androgens; sex hormone binding globulin

Introduction

In men, sex hormones are hypothesized to influence risk for chronic disease such as prostate cancer, cardiovascular disease, benign prostatic hyperplasia, hypertension, diabetes and osteoporosis. (Miller et al., 2001, Institute of Medicine, 2004, Bosland, 2000) Consistent

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predictors of testosterone levels in men include age, race/ethnicity, lean body mass and body mass index (BMI). (Allen et al., 2002, Field et al., 1994, Gapstur et al., under review, Ukkola et al., 2001, Wu et al., 1995) Diet, alcohol and smoking also have been associated with serum testosterone. (Allen et al., 2002, Field et al., 1994, Ukkola et al., 2001)

Despite associations between exercise and testosterone levels in experimental settings (Daly et al., 2005, Smilios et al., 2003, Zmuda et al., 1996), limited observational data exist on the potential associations of either physical activity or cardiovascular fitness with serum testosterone in US men. Most observational data suggest that physical activity is not a major contributor to testosterone levels after controlling for the confounding effects of age, BMI and race. (Allen et al., 2002, Ukkola et al., 2001, Wu et al., 1995, Muller et al., 2003, Svartberg et al., 2003) It is possible that the influence of physical activity might be stronger among men classified as overweight or obese, as some of these men might have higher levels of lean body mass, which is positively associated with androgen levels. No previous study has examined the association of physical activity with androgens across strata of BMI. Furthermore, no observational study has examined the association of long-term changes in physical activity with concurrent changes in androgen concentration.

We examined the cross-sectional associations of serum androgen concentrations with self-reported physical activity and cardiorespiratory fitness, and the association between longitudinal changes in physical activity with concurrent changes in androgens in black and white young men.

Methods

The CARDIA Male Hormone Study

The CARDIA Study is a multi-center, longitudinal study designed to examine physiologic, psychological and lifestyle factors that might affect the development of cardiovascular disease risk factors in young black and white, men and women. Briefly, 5,115 participants, aged 18–30 years, completed a baseline examination in 1985–86 at one of four clinical centers: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; or Oakland, California. Five follow-up examinations were completed in 1987–88 (year two), 1990–91 (year five), 1992–93 (year seven), 1995–96 (year 10), and 2000–01 (year 15). A detailed description of the design, recruitment, and methods of this study was published previously. (Friedman et al., 1988)

A detailed description of the CARDIA Male Hormone Study (CMHS) has previously been published. (Gapstur et al., 2002) Briefly, the study was designed to evaluate longitudinal changes in serum hormone levels in a subset of men (624 black and 796 white). Because we were interested in the relations of physical activity and cardiorespiratory fitness with androgens, our analyses are limited to men in CMHS who provided serum samples at the two examinations (year two and year seven) where physical activity was assessed (1211 men).

Previously, we found total testosterone increases until age 24 years, and then decreases. (Gapstur et al., 2002) Because of this reversal in the relation between age and testosterone concentration, we excluded 198 men who were aged 20–23 at year two. Of the remaining 1013 men, 18 were excluded because they were missing either physical activity or BMI data. The final sample size for this analysis consists of 391 blacks and 604 whites. Other than the expected age difference, there were no significant covariate differences between included and excluded participants. A greater proportion of excluded participants were black (54% of excluded vs 39% of included). The CMHS has been approved by the Institutional Review Board at Northwestern University.

Data Collection

In the CARDIA Study, all 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 hours before each examination. Weight and height were measured using a balance beam scale and a vertical ruler, carpenter's square or stadiometer with participants wearing light clothing and no shoes. Height was recorded to the nearest 0.5 cm and weight to the nearest 0.5 lb. BMI was calculated as the weight (kg) divided by the height squared (m^2). Age and race were self-reported. Cigarette use was assessed by questionnaire. Average daily alcohol intake (milliliters of ethanol per day) was determined from self-reported amount of beer, wine, and liquor consumed per week.

Physical activity

Physical activity was assessed using the CARDIA activity questionnaire (Jacobs et al., 1989, Sidney et al., 1991), an interviewer-administered self-report instrument that assesses frequency of participation over the previous 12 months in eight vigorous intensity and five moderate intensity leisure activities. Reported activities were scored, in exercise units, according to frequency and consistency of participation. A score of 200 exercise units is roughly equivalent to engaging in exercise at six metabolic equivalents (METs) for two hours a week for 11 months of the year. The instrument has been found to have good validity and reliability. (Jacobs et al., 1989, Sidney et al., 1991)

Cardiorespiratory fitness

Fitness was assessed by duration of a symptom-limited graded exercise treadmill test at year seven only. (Sidney et al., 1992) Following a modified Balke protocol, participants were encouraged to push themselves as far as possible. Participants from one test site ($n=313$) were excluded from analyses of fitness because of differences in test administration. An additional 65 participants from other sites did not have data on the exercise treadmill test, leaving 617 in these analyses.

Hormone Measurements

Details of the hormone assessment have been described elsewhere. (Gapstur et al., 2002) Briefly, total testosterone (TT) was measured directly using radioimmunoassay kits and sex hormone binding globulin (SHBG) was measured by chemiluminescent enzyme immunometric assay. The concentrations of bioavailable testosterone (BT) was calculated according to the method of Södergard et al. (Sodergard et al., 1982, Vermeulen et al., 1999) Because there were no associations between time of blood draw and hormone levels in the study (Gapstur et al., under review), time of blood draw was not considered further. Serum concentrations of TT and SHBG appeared normally distributed for both black and white men. Assay variability was monitored by including 10 percent 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 identical to CARDIA participant samples. The intra- and interbatch technical errors were 12.3 and 11.2 percent, respectively, for total testosterone; and 7.9 and 11.2 percent respectively, for SHBG.

Statistical Analysis

Age-adjusted means of participant characteristics at year seven were computed using analysis of covariance. Quartiles of physical activity and cardiorespiratory fitness were determined with black and white men pooled. To assess whether there were associations between physical

activity or cardiorespiratory fitness and androgens, race-specific, multivariable-adjusted mean androgen concentrations were compared among quartiles utilizing ANCOVA. In addition, we used multivariable linear regression to estimate the difference in androgen concentration associated with a 100 unit difference in physical activity score or 100 seconds in cardiorespiratory fitness. The covariates included in the multivariate models were age, BMI, cigarettes smoked, and alcohol intake. For cross-sectional analysis, participants were also classified according to their year seven BMI (normal ($\text{BMI} < 25 \text{ kg/m}^2$), overweight ($25 \leq \text{BMI} < 30 \text{ kg/m}^2$), obese ($\text{BMI} \geq 30 \text{ kg/m}^2$)). We considered an interaction between physical activity or fitness quartile and BMI group. For longitudinal analysis, the five-year changes (year seven – year two) in androgens and in total physical activity were computed, and race-specific linear regression analysis was used to assess their association. Age, change in BMI, cigarettes smoked, and alcohol intake were included as covariates. Additional adjustment for education or medication use did not change the results and, thus, these variables are not included in the analyses.

Results

Most participants were normal (40.4%) or overweight (40.5%) at year seven (Table 1). The mean age was similar across strata of BMI and race. Age-adjusted mean SHBG concentrations were highest among normal weight men (35.6 nmol/L) and lowest among obese men (23.1 nmol/L). TT concentrations were highest among normal weight men and lowest among obese men for both blacks and whites. BT concentrations were similar across strata of BMI. TT concentrations at years two and seven were significantly correlated ($r=0.62$, $p<0.0001$) as were SHBG concentrations ($r=0.72$, $p<0.0001$). Age-adjusted physical activity scores were lowest among obese men. In contrast to physical activity, age-adjusted fitness scores were highest among normal weight men. Most men's physical activity decreased over the five-year period, though some reported an increase (mean change: -41.6 , range: $-1141.0 - 1161.0$). The correlation between fitness and physical activity was 0.26 for blacks and 0.34 for whites ($p<0.001$ for both).

Cross-sectional Associations of Hormones with Physical Activity at Year Seven

In multivariable analyses, physical activity was not associated with concentrations of SHBG, TT or BT in either black or white men (Figure 1). When stratifying by BMI, physical activity quartiles were not associated with SHBG, TT or BT in any race-BMI group (data available upon request from authors). However, in multivariable linear regression average physical activity was statistically significantly associated with TT ($\beta=0.51$, $p=0.04$) and BT ($\beta=0.31$, $p=0.04$) in obese white men only. Average physical activity was not associated with SHBG, TT or BT in any strata of Black men nor among normal and overweight White men. The interaction between physical activity and BMI was not statistically significant for any hormone.

Cross-sectional Associations of Hormones with Cardiorespiratory Fitness at Year Seven

In multivariable analysis, SHBG was significantly ($p=0.05$) associated with fitness among white men with quartiles four and two having the highest (33.5 nmol/L) and lowest (27.8 nmol/L) SHBG concentrations, respectively (Figure 2). TT and BT were not associated with fitness in either blacks or whites. When stratifying by BMI, we found no significant associations between quartiles of fitness and SHBG, TT or BT among black or white men (data available upon request from authors). However, among normal weight white men, a marginally non-significant ($p=0.06$) positive association was found between quartile of fitness and TT. Men with fitness test times of 0–542 seconds had a mean TT concentration of 18.6 nmol/L, while men with times between 754 and 1080 seconds had a mean TT concentration of 20.7 nmol/L. Men with times of 543–643 and 644–753 seconds had TT concentrations of 19.0 nmol/L and 20.0 nmol/L, respectively. In multivariable linear regression, average fitness was significantly

associated with SHBG among both black ($\beta=1.27$, $p=0.05$) and white ($\beta=1.07$, $p=0.05$) men. When stratifying by BMI, among white men, SHBG was statistically significantly associated with average fitness only among normal ($\beta=2.20$, $p=0.01$) and obese ($\beta=3.87$, $p=0.007$) men. TT was significantly associated with average fitness only among normal weight white men ($\beta=0.77$, $p=0.03$) whereas BT was not associated with average fitness in any race-BMI group. Among black men, there were no significant associations between average fitness and androgens in any BMI strata. However, there was a borderline significant association between SHBG and fitness in obese black men ($\beta=2.44$, $p=0.06$). Importantly, there was no interaction between fitness and BMI for any hormone.

Longitudinal Associations of Hormones with Change in Physical Activity

In multivariable longitudinal analyses, change in physical activity was not associated with change in SHBG, TT or BT in white men or in black men (Table 2). Among white men, in age-adjusted analysis, for every 100 unit change in physical activity between year two and year seven, there was a 0.19 nmol/L increase in TT ($p=0.03$). This association was attenuated and became non-significant after adjustment for covariates. There was no association between change in physical activity and hormones in strata of BMI stability (data not shown).

Discussion

This observational study is the largest to date to investigate the association between longitudinal changes in self-reported physical activity and testosterone in men. It is also the first to investigate the association between physical activity and fitness with androgens across strata of BMI. There was no association of physical activity with SHBG, TT or BT concentration in blacks or whites overall. Interestingly, fitness was significantly associated with SHBG concentration in normal weight and obese whites, whereas no consistent association was found in blacks nor were associations of fitness and either TT or BT found. Additionally, there were no statistically significant interactions between BMI and either fitness or physical activity on hormone levels in cross-sectional analyses. In longitudinal analysis, hormones were not associated with change in physical activity among black or white men.

At least two previous cross-sectional studies found positive associations between physical activity and androgen levels (Allen et al., 2002, Muller et al., 2003), but others found no association (Bonney et al., 1998, Mantzoros and Georgiadis, 1995, Svartberg et al., 2003, Ukkola et al., 2001, Wu et al., 1995). For example, Allen et al found vigorous exercise for three or more hours/week was positively associated with testosterone and SHBG, but not free testosterone among men (Allen et al., 2002). Variation in findings across studies could arise from differences in the questionnaires used to assess physical activity, covariates included in analyses, or intensity of physical activity levels across study populations.

Previous studies consistently show inverse associations between BMI and both TT and SHBG, likely owing to the greater lean body mass among normal weight men (Couillard et al., 2000, Gapstur et al., 2002, Gray et al., 1991, Wu et al., 1995). Previous studies of physical activity and androgens did not stratify participants by BMI, but most included it as a covariate. We found no significant interactions between BMI and either physical activity or fitness.

Few cross-sectional studies investigated the association between measured cardiovascular fitness and androgens in non-elite athletes. In one observational study that did not adjust for BMI, no association was observed between fitness and testosterone (Bonney et al., 1998). The biologic mechanism underlying the potential association between fitness and SHBG is unknown. It is possible that self-reported physical activity might represent of long term physical activity patterns consistently performed over many years, whereas cardiorespiratory fitness reflects current physical activity status. Therefore, fitness might be more strongly associated

with physiologic factors as it is a more accurate indicator of current physical activity compared to self-reported physical activity. Moreover, since physical activity is inversely associated with insulin, which is itself inversely associated with SHBG (Plymate et al., 1988), it is possible that the objectively measured fitness variable may better correlate with SHBG, and the effects of physical activity may be indirectly mediated through fitness and insulin.

Change in physical activity from year two to year seven was not associated with change in hormones. We are aware of only one other observational study that examined longitudinal changes in physical activity and testosterone.(Bonney et al., 1998) That study of 16 elderly men examined six-month changes in questionnaire assessed physical activity and found no significant associations with change in TT. In combination, these results support the conclusion that change in physical activity is unlikely to be an important determinant of changing testosterone levels.

Strengths and Limitations

This study has several strengths. Serially collected hormone measurements allowed the novel study of the effects of long-term changes in physical activity on changes in hormones. Additionally, this is the first study that we are aware of to assess the association of cardiorespiratory fitness and hormone concentrations in a large observational setting. Regardless, certain factors should be considered in interpreting our data. Physical activity was self reported and might not capture all activities relevant to the associations under study. Furthermore, while the questionnaire was found to be reliable and valid, white men had higher fitness scores but lower physical activity scores than black men. Because of these differences, our cross-sectional analyses were stratified by race which led to small numbers of subjects in some cells. We were unable to examine longitudinal changes in fitness and their associated changes with androgens because the two were measured at the same examination only once (year seven). Fitness was assessed only on a subset of men (n=617). These men did not significantly differ from the rest of the sample in hormone levels or physical activity, but were significantly younger (p=0.04). The small volume of serum available precluded direct measurement of BT, but our computational approach is considered valid.(23) Finally, the cross-sectional nature of our findings precludes any conclusions on causation or temporality.

Conclusion

Physical activity does not appear to be an important determinant of serum androgen concentrations. Cardiorespiratory fitness is associated with SHBG levels, but does not appear to be an important determinant of BT or TT levels. Overall the results do not support a major role for exercise in determining androgen levels in young men.

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Figure 1. Age, BMI, cigarette use, and alcohol intake adjusted mean hormone levels by quartile of total physical activity for black and white men, CARIDA Male Hormone Study, Year Seven (1992–1993)

Figure 2. Age, BMI, cigarette use, and alcohol intake adjusted mean hormone levels by quartile of cardiorespiratory fitness for black and white men, CARIDA Male Hormone Study, Year Seven (1992–1993)

Table 1
Subject characteristics by race and BMI at Year Seven (1992–1993) exam, CARDIA

	All subjects*			Black men			White men		
	Normal**	Overweight	Obese	Normal	Overweight	Obese	Normal	Overweight	Obese
N	402	403	190	135	152	104	267	251	86
Mean age	33.0	33.2	33.0	32.6	32.9	33.1	33.2	33.5	32.8
Age adjusted mean									
Total testosterone (nmol/L)	21.9	19.8	17.1	22.6	20.1	17.2	21.4	19.5	17.0
Bioavailable testosterone (nmol/L)	10.1	10.2	9.5	10.6	10.4	9.5	9.7	10.0	9.6
SHBG (nmol/L)	35.6	28.9	23.1	36.1	29.0	23.9	35.2	28.6	22.1
Cardiorespiratory fitness, minutes	698.4	626.8	540.2	651.0	591.9	522.6	740.8	661.9	554.8
Total activity score	448.0	452.8	386.8	468.7	475.8	433.3	423.6	427.7	340.1
Waist circumference, cm	79.2	89.7	105.5	77.5	88.7	104.1	80.6	90.8	106.9
BMI, kg/m ²	22.7	27.1	33.9	22.4	27.2	34.1	22.8	27.0	33.7

* values are also race adjusted

** Normal (BMI < 25 kg/m²), Overweight (25 ≤ BMI < 30 kg/m²), Obese (BMI ≥ 30 kg/m²)

CARDIA – Coronary Artery Risk Development in Young Adults Study

BMI – body mass index

SHBG – sex hormone binding globulin

L – liter

cm – centimeter

kg/m² – kilograms/meter²

Longitudinal association of change in hormone levels from Year Two (1987–1988) to Year Seven (1992–1993) with change in total physical activity for black and white men, CARDIA

	SHBG		TT		BT	
	nmol/L, se	p-value	nmol/L, se	p-value	nmol/L, se	p-value
Blacks						
Age adjusted	0.08, 0.15	0.58	0.13, 0.09	0.15	0.04, 0.06	0.47
Multivariable adjusted**	0.01, 0.15	0.94	0.06, 0.09	0.48	0.02, 0.06	0.79
Whites						
Age adjusted	0.15, 0.16	0.35	0.19, 0.09	0.03	0.06, 0.06	0.31
Multivariable adjusted**	0.07, 0.15	0.64	0.13, 0.09	0.13	0.04, 0.06	0.51

* Beta represents change in hormone level associated with a 100 unit change in PA

** Adjusted for age, BMI, cigarette use and alcohol intake

CARDIA – Coronary Artery Risk Development in Young Adults Study

SHBG – sex hormone binding globulin

TT – total testosterone

BT – bioavailable testosterone

PA – physical activity

BMI – body mass index

se – standard error