

Inverse Association of Testosterone and the Metabolic Syndrome in Men Is Consistent across Race and Ethnic Groups

Varant Kupelian, Frances J. Hayes, Carol L. Link, Raymond Rosen, and John B. McKinlay

New England Research Institutes (V.K., C.L.L., R.R., J.B.M.), Watertown, Massachusetts 02472; and Massachusetts General Hospital (F.J.H.), Boston, Massachusetts 02114

Context: Low sex hormone levels have been associated with the metabolic syndrome (MetS).

Objectives: Our objective was to determine whether the association between sex hormone levels and MetS varies by race/ethnicity among men and to investigate the relationship of sex hormones and individual components of MetS.

Design: We conducted a population-based observational survey.

Participants: A multistage stratified design was used to recruit a random sample of 2301 racially/ethnically diverse men age 30–79 yr. Blood samples were obtained on 1899 men. Analyses were conducted on 1885 men with complete data on total testosterone (T), free T, and SHBG.

Interventions: There were no interventions.

Main Outcome Measure: MetS was defined using a modification of the Adult Treatment Panel III guidelines. The association between MetS and sex hormone levels was assessed using odds ratios and 95% confidence intervals estimated using logistic regression models.

Results: A strong inverse association was observed, in both bivariate and multivariate analyses, between hormone levels and MetS. The odds of MetS increased about two-fold with a 1 SD decrease in hormone levels. The association between sex hormones and MetS was statistically significant across racial/ethnic groups. Although the magnitude of this association was largest among White men, racial/ethnic differences were not statistically significant. The strength of the association of sex hormones with individual components of MetS varied; stronger associations were observed with waist circumference and dyslipidemia and more modest associations with diabetes and elevated blood sugar.

Conclusions: A robust, dose-response relationship between sex hormone levels and odds of the metabolic syndrome in men is consistent across racial/ethnic groups. (*J Clin Endocrinol Metab* 93: 3403–3410, 2008)

The metabolic syndrome (MetS), a constellation of cardiovascular risk factors thought to be linked by insulin resistance (1), is characterized by dyslipidemia, hyperglycemia, hypertension, and central obesity. MetS has been established as a precursor state in which patients are at a significantly increased risk of developing cardiovascular disease (2, 3).

Aging is associated with a gradual decline in testosterone (T) levels in men (4, 5). This decrease is accompanied by changes in body composition including increases in fat mass and decreases in lean body mass, dyslipidemia, insulin resistance, and glucose metabolism dysregulation (6–10). Epidemiological evidence has shown that sex hormones are related to type 2 diabetes and cardiovascular disease in men

0021-972X/08/\$15.00/0

Printed in U.S.A.

Copyright © 2008 by The Endocrine Society

doi: 10.1210/jc.2008-0054 Received January 8, 2008. Accepted June 6, 2008.

First Published Online June 17, 2008

Abbreviations: ATP, Adult Treatment Panel; BACH, Boston Area Community Health; BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; MetS, metabolic syndrome; OR, odds ratios; T, testosterone.

in some, but not all, studies (7, 11–14). Low serum T and SHBG have been associated with MetS both cross-sectionally and longitudinally (15–19). However, whether this association varies by race/ethnicity has not been reported previously.

Using data from the Boston Area Community Health (BACH) survey, the relationship between sex hormones and MetS can be investigated in a large population-based racially and ethnically diverse sample. The objectives of this analysis are to determine whether the associations between sex hormones and MetS vary by race/ethnicity and to investigate the relationship of sex hormones and individual components of MetS.

Subjects and Methods

Overall design

The BACH survey is a population-based epidemiological survey of a broad range of urological symptoms and risk factors in a randomly

selected sample. Detailed methods have been described elsewhere (20). In brief, BACH used a multistage stratified random sample to recruit approximately equal numbers of subjects according to age (30–39, 40–49, 50–59, 60–69, and 70–79 yr), gender, and racial and ethnic group [African-American (Black), Hispanic, and Caucasian (White)]. The BACH sample was recruited from April 2002 through June 2005. Interviews were completed with 63.3% of eligible subjects, resulting in a total sample of 5503 adults (2301 men, 3203 women, 1767 Black, 1877 Hispanic, and 1859 White respondents). All protocols and informed consent procedures were approved by the New England Research Institutes' Institutional Review Board.

Data collection

Data were obtained during a 2-h in-person interview, conducted by a trained (bilingual) phlebotomist/interviewer, generally in the subject's home. After written informed consent, a venous blood sample (20 ml) was obtained, and height, weight, and hip and waist circumference were measured along with self-reported information on medical and reproductive history, major comorbidities, lifestyle and psychosocial factors, and symptoms of urogynecological conditions. Two blood pressure mea-

TABLE 1. Descriptive characteristic of analysis sample, overall and by race/ethnicity

Variable	n (weighted %)				P value ^b
	Overall, n = 1885	White, n = 706	Black, n = 530	Hispanic, n = 649	
Age (yr)					
30–39	509 (38.3)	174 (37.2)	126 (36.4)	209 (47.1)	<0.001
40–49	548 (26.7)	185 (25.4)	169 (28.9)	194 (29.2)	
50–59	435 (18.0)	167 (17.7)	129 (20.7)	139 (14.9)	
60–69	257 (10.7)	109 (12.2)	72 (9.6)	76 (5.6)	
70–79	136 (6.2)	71 (7.5)	34 (4.5)	31 (3.3)	
BMI (kg/m ²)					
<25	490 (26.7)	192 (26.9)	143 (26.4)	155 (26.4)	0.132
25–29	735 (39.8)	281 (41.8)	185 (33.6)	268 (41.3)	
≥30	658 (33.5)	231 (31.3)	202 (40.0)	225 (32.2)	
Smoking					
Never	808 (45.9)	302 (45.2)	207 (44.7)	299 (51.7)	0.003
Former	538 (28.4)	228 (31.9)	119 (21.9)	191 (23.2)	
Current	538 (25.6)	176 (22.9)	204 (33.3)	158 (25.1)	
Physical activity (PASE)					
Low (<100)	530 (25.0)	209 (26.2)	142 (22.2)	179 (24.7)	0.552
Medium (100–250)	895 (48.3)	333 (49.0)	243 (46.6)	317 (48.1)	
High (>250)	459 (26.6)	163 (24.8)	144 (31.3)	151 (27.2)	
Alcohol consumption					
None	633 (25.7)	187 (21.4)	188 (33.1)	258 (33.0)	<0.001
<1/d	688 (40.4)	280 (42.4)	175 (35.3)	233 (40.0)	
1–3/d	359 (24.8)	177 (28.3)	89 (19.3)	93 (17.6)	
3+/d	203 (9.1)	61 (7.9)	78 (12.2)	64 (9.4)	
Sex hormones, mean (sd)					
Total T (ng/dl)	436 (183)	432 (175)	444 (197)	441 (189)	0.718
Free T (ng/dl)	9.1 (3.8)	8.9 (3.6)	9.2 (4.1)	9.5 (4.1)	0.193
SHBG (nmol/liter)	34.1 (17.8)	34.1 (16.6)	35.4 (21.1)	31.9 (16.2)	0.045
Log SHBG	3.41 (0.48)	3.42 (0.47)	3.42 (0.53)	3.36 (0.45)	0.146
MetS components					
Diabetes/elevated blood sugar/diabetes medication use	281 (11.5)	71 (9.4)	92 (15.2)	117 (14.5)	0.026
Hypertension ^a	997 (46.8)	351 (42.2)	339 (61.1)	307 (41.8)	<0.001
HDL < 40 mg/dl or lipid medication use	771 (39.8)	306 (41.7)	174 (35.8)	291 (38.5)	0.368
Triglycerides > 150 mg/dl	860 (41.9)	330 (44.6)	164 (30.0)	366 (51.7)	<0.001
Waist > 102 cm	619 (33.4)	256 (34.9)	169 (32.8)	194 (27.0)	0.095
MetS	607 (29.0)	220 (28.6)	157 (30.5)	230 (28.4)	0.805

PASE, Physical Activity Scale for the Elderly.

^a Systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mmHg or antihypertensive use.

^b For categorical variables, *P* values are from χ^2 tests of independence between the racial/ethnic groups, and for continuous variables, *P* values are from *F* tests comparing means by the racial/ethnic groups.

surements were obtained during the interview and were averaged. BACH participants were asked to gather all prescription, over-the-counter, and alternative medications in the home used by them over the past 4 wk for recording of the label information by the interviewer. Additionally, participants were asked separately whether they were taking medication for specific indications, such as high cholesterol and high blood pressure.

Hormones

Nonfasting blood samples were collected close to waking time (median time since awakening, 3 h 38 min) to control for diurnal variation in hormone levels. T and SHBG were measured by competitive electrochemiluminescence immunoassays on the 2010 Elecsys system (Roche Diagnostics, Indianapolis, IN). All assays were previously approved by the Food and Drug Administration for clinical use. The lower limits of detection for testosterone and SHBG were 2 ng/dl (0.07 nmol/liter) and 3 nmol/liter, respectively. Reference ranges are 260–801 ng/dl (9–27.8 nmol/liter) for T and 14.5–48.4 nmol/liter for SHBG. The interassay coefficients of variation for T at concentrations of 24, 275, and 700 ng/dl (0.8, 9.5, and 24.3 nmol/liter) were 7.4, 2.2, and 1.7%, respectively. For SHBG at 16.5, 25, and 64 nmol/liter, interassay coefficients of variation were 3.9, 2.4, and 2.2%, respectively. Free T concentrations were calculated from total T and SHBG concentrations using mass action equations (21, 22).

MetS definition

The concept of the MetS refers to a constellation of cardiovascular risk factors. The components of MetS, including dyslipidemia, elevated blood pressure, impaired glucose tolerance, and central obesity, are thought to be linked by insulin resistance (1). MetS was first operationally defined by a World Health Organization Consultant Group (23) and subsequently refined by a National Institutes of Health Expert Panel [National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines] (24). Modifications of MetS criteria have been proposed by the European Group for Study of Insulin Resistance (EGIR) (25), the American Association of Clinical Endocrinologists (26), and the International Diabetes Foundation (27). A recent joint statement from the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) upheld the ATP III criteria with minor modifications (28). Available BACH data permit close adherence to the ATP III guidelines with the major exception that usually nonfasting blood samples were available for analyses, impacting analyses of triglycerides and fasting glucose. For the purpose of this analysis, MetS was defined, using a previously published modification of the ATP III guidelines (15, 16), as the presence of three or more of the following: 1) waist circumference more than 102 cm; 2) systolic blood pressure at least 130 mm Hg or diastolic blood pressure at least 85 mm Hg or antihypertensive medication use; 3) high-density lipoprotein (HDL) cholesterol less than 40 mg/dl or lipid medication use; 4) self-reported type 2 diabetes or elevated blood sugar or diabetes medication use; and 5) triglycerides more than 150 mg/dl.

Covariates

Potential confounders included in the analysis include sociodemographic and lifestyle factors, in addition to comorbid conditions and sex hormone levels. The following covariates were considered as categorical variables. Age was categorized by decade: 30–39, 40–49, 50–59, 60–69, and 70–79 yr. Self-reported race/ethnicity was defined as Black, Hispanic, or White. Body mass index (BMI) was categorized as less than 25, 25–29, and 30 kg/m² or higher. Physical activity was measured using the Physical Activity Scale for the Elderly (PASE) and was categorized as low (<100), medium (100–250), and high (>250). Alcohol consumption was defined as alcoholic drinks including beer, wine, and hard liquor consumed per day: zero, fewer than one, one to three, or more than three drinks per day. Smoking was defined as never smokers (smoked fewer than 100 cigarettes lifetime and not currently smoking), former smokers (smoked >100 cigarettes lifetime and currently nonsmoker), and current smokers (smoked >100 cigarettes and currently a smoker).

Statistical analysis

Descriptive statistics, proportions for categorical variables, and mean and SD for continuous variables were used to describe the analysis sample. Serum hormone levels were analyzed both as continuous variables and were grouped into quartiles of their distributions. Because the distribution of SHBG concentrations was skewed, log-transformed values of SHBG levels were used. Multiple logistic regression models were used to assess the association between sex hormones and MetS and to adjust for potential confounders. Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated to describe the magnitude of the association. OR were reported per change in 1 SD for hormone levels. Of the 2301 male participants, blood samples were obtained for 1899 (82.5%). After excluding men with missing or extreme values for T and SHBG, 1885 men were included in the analysis. A multiple imputation technique was used to obtain plausible variables for missing data (29). Of the 1885 men included in the analysis, 43 (2.2%) had missing data on one or more covariates, with the largest amount of missing data reported for the physical activity measure for 17 (0.9%) men. Twenty-five multiple imputations were performed separately by race/ethnicity using all relevant variables. Observations were weighted as inversely proportional to their probability of selection (30). Weights were post-stratified to the Boston population according to the 2000 census. Analyses were conducted in version 9.1 of SAS (SAS Institute, Cary, NC) and version 9.0.1 of SUDAAN (Research Triangle Institute, Research Triangle Park, NC).

Results

Characteristics of the 1885 men in the sample are presented in Table 1 by racial/ethnic groups. Hispanic men were younger [mean age 44.2 ± 10.8 yr (mean ± 1 SD)] compared with both White men (48.1 ± 13.0 yr) and Black men (47.7 ± 12.0 yr),

TABLE 2. Association of potential confounders and the MetS: OR and 95% CI

Variable	OR ^a (95% CI)	P value
Age (yr)		
30–39	1.00	<0.001
40–49	1.64 (0.95–2.85)	
50–59	2.41 (1.45–4.02)	
60–69	4.08 (2.48–6.72)	
70–79	2.51 (1.34–4.69)	
Race/ethnicity		
White	1.00	0.737
Black	1.12 (0.78–1.60)	
Hispanic	1.16 (0.79–1.70)	
Physical activity (PASE)		
Low (<100)	1.00	<0.001
Medium (100–250)	0.52 (0.35–0.79)	
High (>250)	0.35 (0.21–0.58)	
Alcohol consumption		
None	1.00	<0.001
<1/d	0.89 (0.62–1.29)	
1–3/d	0.35 (0.22–0.55)	
3+/d	0.79 (0.34–1.81)	
Smoking		
Never	1.00	0.454
Former	1.28 (0.87–1.87)	
Current	1.16 (0.73–1.84)	

PASE, Physical Activity Scale for the Elderly.

^a OR for race/ethnicity, physical activity, alcohol consumption, and smoking are adjusted for age.

reflecting the age distribution by race/ethnicity in the Boston population. Prevalence of obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) was higher among Black men (40%) compared with White men (31.3%) and Hispanic men (32.2%). A larger proportion of Black men were current smokers (33.3%) compared with White (22.9%) and Hispanic men (25.2%), whereas physical activity levels were comparable by race/ethnicity. As previously reported (31), serum hormone levels did not differ by race/ethnicity. Prevalence of MetS was 29% overall and did not differ by race/ethnicity. Prevalence of type 2 diabetes or self-reported elevated blood sugar was higher among Black (15.2%) and Hispanic men (14.5%) compared with White men (9.4%), whereas hypertension (as described in MetS definition) was higher among Black men (61.1%) compared with White (42.2%) and Hispanic men (41.8%). In contrast, prevalence of elevated triglycerides was lower among Black men (30%) compared with White (44.6%) and Hispanic Men (51.7%).

The association of potential risk factors and MetS are presented in Table 2. Age was a strong predictor of MetS with OR increasing with age, except for the oldest age group. OR for race/ethnicity, smoking, alcohol consumption, and physical activity were adjusted for age. Race/ethnicity and smoking were not associated with MetS, whereas higher physical activity and moderate alcohol consumption were associated with lower odds of MetS.

Figure 1 shows the adjusted means with 95% CI for total T, free T, and SHBG for zero, one, two, or three or more components of MetS. A significant trend in decreasing levels of circulating sex hormones with increasing number of MetS components was observed. For both total T and SHBG, the largest decrease in mean hormone concentrations was observed between the presence of one *vs.* the presence of two components of MetS with changes from 474 ng/dl (95% CI, 451–498) to 389 ng/dl (95% CI, 366–412) for total T and from 37.4 nmol/liter (95% CI, 35.5–39.4) to 30.6 nmol/liter (95% CI, 28.9–32.3) for SHBG. Means were adjusted for age, race/ethnicity, physical activity, smoking, and alcohol consumption (Fig. 1).

A strong inverse association was observed, both in bivariate and multivariate analyses, between hormone levels and MetS, with odds of MetS increasing with decreasing levels of total T, free T, and SHBG (Table 3). Odds of MetS increased about 2-fold with a 1 SD decrease in hormone levels. Adjusted OR for the lowest quartiles compared with the highest quartiles of the distribution of sex hormone levels were 8.35 (95% CI, 4.68–14.90) for total T, 5.74 (95% CI, 3.14–10.51) for free T, and 10.53 (95% CI, 5.64–19.65) for SHBG. Stratified analyses by racial/ethnic groups show that results are consistent across racial/ethnic groups with statistically significant associations between sex hormones and MetS within each group (Fig. 2). Although the magnitude of the sex hormone and MetS association was largest

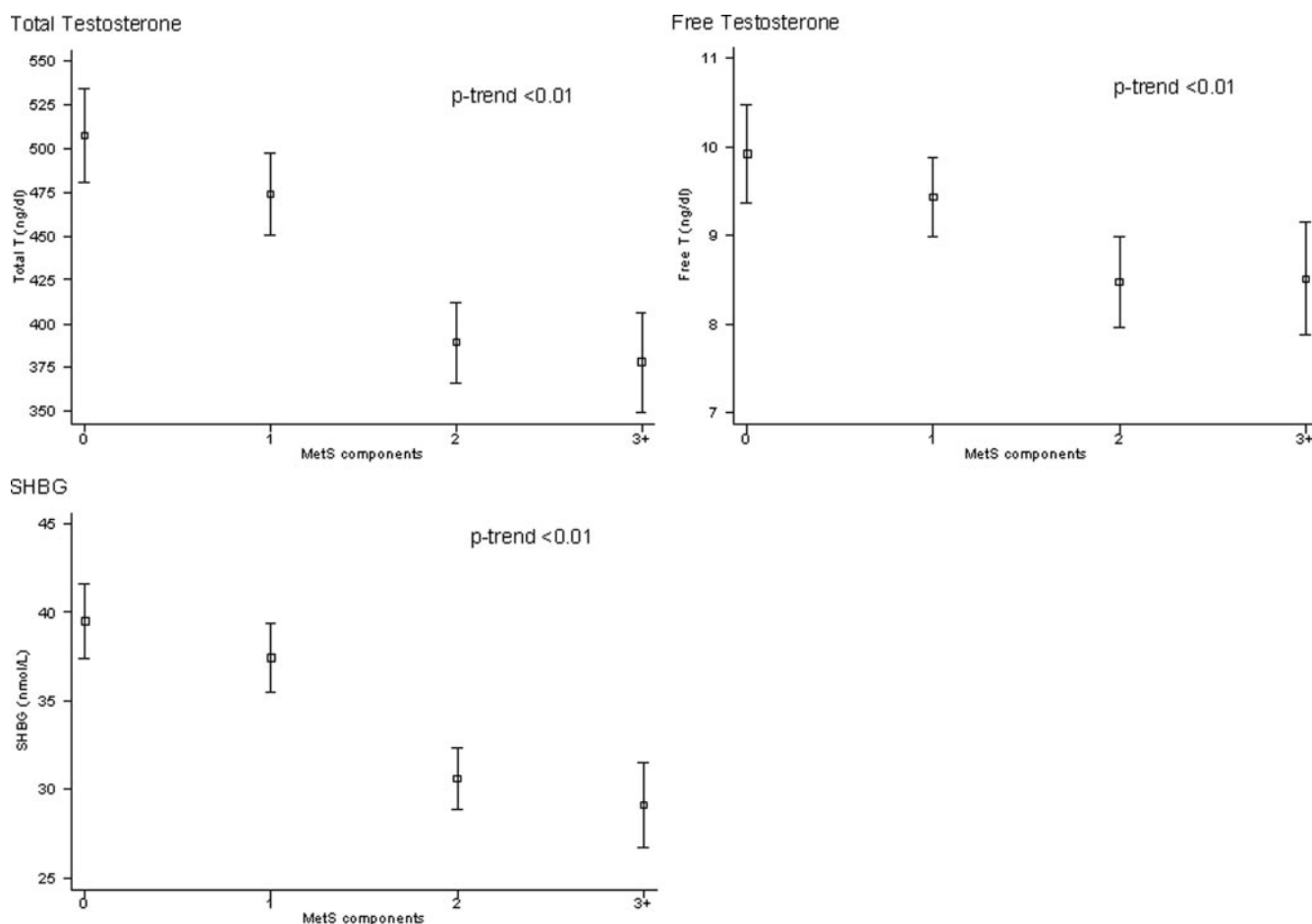


FIG. 1. Adjusted means and 95% CI for sex hormone levels by number of components of MetS. Mean hormone levels were adjusted for race, age, physical activity, alcohol consumption, and smoking.

TABLE 3. Association of sex hormones and the metabolic syndrome. OR and 95% CI

	Unadjusted OR (95% CI)	Adjusted ^a OR (95% CI)
Total T (ng/dl)		
–1 SD (183)	2.36 (1.91–2.91)	2.37 (1.88–2.97)
Quartiles		
>75%	1.00	1.00
50–75%	2.33 (1.32–4.12)	2.24 (1.31–3.86)
25–50%	3.63 (2.21–5.99)	3.61 (2.15–6.06)
<25%	8.23 (4.79–14.12)	8.35 (4.68–14.9)
Free T (ng/dl)		
–1 SD (3.8)	2.09 (1.66–2.63)	1.87 (1.45–2.41)
Quartiles		
>75%	1.00	1.00
50–75%	2.69 (1.63–4.44)	2.64 (1.58–4.4)
25–50%	4.32 (2.56–7.29)	3.46 (2.04–5.87)
<25%	6.81 (3.97–11.7)	5.74 (3.14–10.51)
Log SHBG (nmol/liter)		
–1 SD (0.48)	1.57 (1.33–1.84)	2.46 (1.95–3.1)
Quartiles		
>75%	1.00	1.00
50–75%	1.26 (0.81–1.96)	1.53 (0.94–2.49)
25–50%	1.42 (0.93–2.19)	3.35 (1.95–5.77)
<25%	3.25 (2.07–5.09)	10.53 (5.64–19.65)

^a Adjusted for age, race/ethnicity, physical activity, smoking, and alcohol consumption.

among White men, racial/ethnic differences were not statistically significant.

The relationship of sex hormones and components of MetS was presented in Table 4. The strongest associations with sex hormones were observed for triglycerides higher than 150 mg/dl and waist circumference more than 102 cm with OR ranging between 1.5 and 2.4 per 1 SD decrease, whereas OR were more modest with hypertension (OR ranging between 1.27 and 1.35). Total T and free T were associated with diabetes/elevated blood sugar (OR of 1.50 and 1.70, respectively, per 1 SD decrease), but SHBG was not (OR = 1.22; 95% CI, 0.91–1.64). Increased odds of low HDL (<40 mg/dl) were observed with lower total T levels (OR =

1.53) and SHBG (OR = 2.13) but not with free T (OR = 1.17; 95% CI, 0.94–1.46). Further adjusting for BMI, observed associations of sex hormones and MetS were attenuated but remained statistically significant with the exception of the associations observed with hypertension. Because waist circumference and BMI are strongly correlated (linear correlation of 0.87), the association of sex hormones and waist circumference was not adjusted for BMI. These results were largely consistent by race/ethnicity with the exception of T levels (both total and free) among Hispanic men not being associated with both diabetes/elevated blood sugar and hypertension.

Discussion

Results from the BACH survey, in a large population-based random sample of 1885 men, show a strong dose-response relationship between decreased levels of sex hormones and increased odds of MetS, consistent with findings from other studies. This robust effect was observed across all three race/ethnic groups assessed, a finding that to our knowledge has not been reported previously. The increased odds of MetS with lower T and SHBG levels was consistent by racial/ethnic groups and persisted after adjusting for age, physical activity, smoking, and alcohol consumption.

Low levels of circulating sex hormones have been associated with risk factors for MetS such as central adiposity (18, 32), insulin resistance (33, 34), and unfavorable lipid profile (10, 35). In a cross-sectional study, Muller *et al.* (18) found a decrease in the odds of MetS with increasing levels of total T and SHBG after controlling for important risk factors. These results were replicated in a longitudinal study by Laaksonen *et al.* (17) with a 2-fold increase in the risk of incident MetS for the lowest quartiles of T compared with the highest quartiles independent of major risk factors. Results of longitudinal analyses of the Massachusetts Male Aging Study over a period of 15 yr showed that low serum T and SHBG levels were predictive of incident MetS

particularly among men with BMI less than 25 with adjusted relative risks of 1.41 (95% CI, 1.06–1.87) for a decrease of 1 SD in total T and 1.65 (95% CI, 1.12–5.65) for SHBG (15). More recently, data from the Baltimore Longitudinal Study of Aging have reported similar results with increasing levels of both total T and SHBG being associated with decreased risk of incident MetS (19).

Because BACH is presently a cross-sectional study, the temporal sequence between low hormone levels and development of MetS cannot be established. However, as illustrated in Fig. 1, a larger decrease in both total T and SHBG levels is observed between having one component of MetS *vs.* two components. In contrast, the decrease is smallest going from two components to actual MetS with the presence of three or more components. This suggests that sex hormone levels

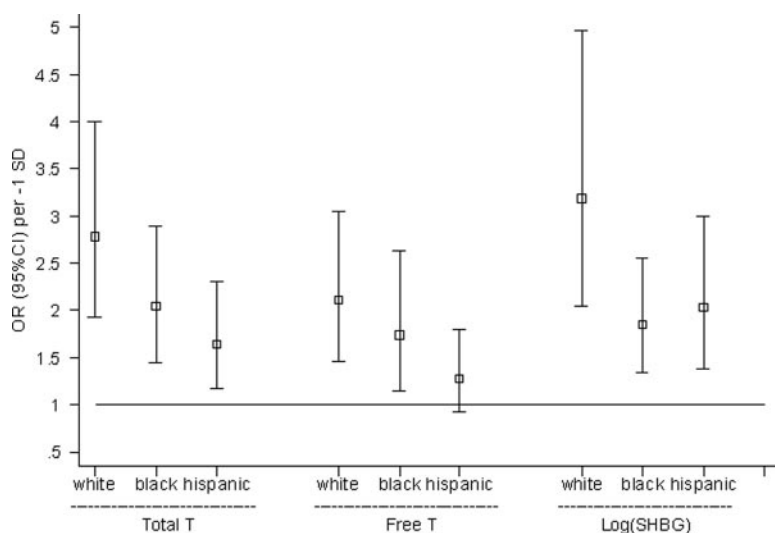


FIG. 2. Association of sex hormones and MetS by racial and ethnic groups. OR and 95% CI are shown per decrease in 1 SD, adjusted for age, physical activity, smoking, and alcohol consumption.

TABLE 4. Association of sex hormones with components of the metabolic syndrome. Adjusted odds ratios and 95% confidence intervals

Model	Type 2 diabetes/elevated blood sugar/ diabetes medication use	Hypertension/ antihypertensive medication use	HDL < 40 mg/dl/lipid medication use	Triglycerides > 150 mg/dl	Waist > 102 cm
Total T (ng/dl), –1 SD = 183					
A ^a	1.50 (1.14–1.96)	1.35 (1.13–1.61)	1.53 (1.26–1.87)	1.86 (1.52–2.28)	2.40 (1.97–2.93)
B ^b	1.30 (1.00–1.69)	1.06 (0.89–1.27)	1.33 (1.10–1.62)	1.64 (1.35–1.99)	
Free T (ng/dl), –1 SD = 3.8					
A ^a	1.70 (1.38–2.09)	1.33 (1.10–1.61)	1.17 (0.94–1.46)	1.50 (1.19–1.91)	1.97 (1.58–2.44)
B ^b	1.50 (1.20–1.88)	1.12 (0.93–1.34)	1.03 (0.84–1.27)	1.34 (1.08–1.68)	
Log SHBG (nmol/liter), –1 SD = 0.48					
A ^a	1.22 (0.91–1.64)	1.27 (1.06–1.52)	2.13 (1.74–2.61)	2.03 (1.67–2.46)	2.13 (1.79–2.53)
B ^b	1.08 (0.80–1.45)	1.00 (0.83–1.21)	1.92 (1.58–2.34)	1.80 (1.49–2.17)	

^a OR adjusted for age, race/ethnicity, physical activity, smoking, and alcohol consumption.

^b OR adjusted for age, race/ethnicity, physical activity, smoking, alcohol consumption, and BMI. BMI was not included in the model for waist >102 cm because waist circumference and BMI are very strongly correlated.

may decrease substantially before the development of MetS. Examination of the relationship between sex hormone levels and individual components of MetS indicate that lower hormone concentrations are more strongly associated with abdominal obesity and dyslipidemia, whereas the association with diabetes/elevated blood sugar was more modest and the association with hypertension did not hold after adjusting for BMI. A similar pattern was reported by Muller *et al.* (18) for the associations between testosterone levels and components of MetS. Although weight loss and weight maintenance have been shown to increase free and total T and SHBG levels in obese men and men with MetS and abdominal obesity (36, 37), interventional studies of exogenous T supplementation in men with low serum T levels have shown increases in lean mass and decreases in fat mass, total cholesterol, and low-density lipoprotein (38–41). Thus, it is likely that the relationship of sex hormones and MetS is to some degree bidirectional with low sex hormone being predictive of the development of MetS, which in turn is associated with further decline in sex hormone levels.

Experimental studies have shown an impact of T on fat metabolism mediated largely by stimulation of β -adrenergic-induced lipolysis. *In vitro*, T enhances lipolysis by increasing the number of β -adrenergic receptors on rat adipocyte precursor cells (42). Similarly, castration of male rats causes a decrease in lipolysis that is reversed by physiological T replacement (43). In two small studies conducted in men with central adiposity, T has been shown to inhibit lipoprotein lipase activity in abdominal adipose tissue, leading to decrease triglyceride uptake in central fat depots (44, 45). In addition, studies using radiolabeled oleic acid indicate that T increases triglyceride turnover in abdominal but not femoral tissue (44).

The relationship between sex hormones and MetS among minority populations has not been reported previously. Previous analyses of BACH data have shown no difference in sex hormone levels by race and ethnic groups (31). Results from the present analysis show that there is a statistically significant association between sex hormones and MetS across racial/ethnic groups; the magnitude of the observed OR was larger among White men

compared with minority populations, although the difference was not statistically significant (Fig. 2). A similar pattern was observed in the associations between sex hormones and individual components of MetS. These results were largely consistent by race/ethnicity with the exception of T levels (both total and free) among Hispanic men not being associated with diabetes/elevated blood sugar.

Several potential study limitations should be noted. Because fasting blood samples were not obtained, available data permit close approximation, but not perfect adherence, to the ATP III guidelines for the definition of MetS (15, 16). Despite this recognized limitation, the approach used in this paper has scientific merit because 1) the ATP III components have always been suggested guidelines, not an immutable clinically validated definition; 2) there is continuing debate over which components of MetS should be included, removed, or added; 3) it is employed as a concept for purposes of epidemiological analysis rather than for clinical purposes. The feasibility of mandating fasting blood samples is cost and resource prohibitive given the original BACH design. The benefits of using data from a large population-based sample outweigh the recognized limitation associated with the measurement of some components of MetS. The BACH study was limited geographically to the Boston area. However, comparison of sociodemographic and health-related variables from the BACH survey with other large regional [Boston Behavioral Risk Factor Surveillance System (BRFSS)] and national (National Health Interview Survey, National BRFSS) surveys have shown the BACH estimates are comparable on health-related variables. Strengths of the BACH study include a community-based random sample across a wide age range (30–79 yr), inclusion of large numbers of minority participants representative of both the Black and Hispanic populations, and collection of a broad number of covariates on sociodemographic, lifestyle, and health factors that can be adjusted for in the analysis.

In summary, results from the BACH study demonstrate an inverse association between sex hormones and MetS, with a strong dose-response relationship between decreasing levels of T and SHBG and increased odds of MetS. This association is con-

sistent across racial/ethnic groups and persists after controlling for important confounding factors. Association of sex hormones with individual components of MetS was stronger with abdominal obesity and dyslipidemia and was more modest with diabetes.

Acknowledgments

Address all correspondence to: Varant Kupelian, Research Scientist, 9 Galen Street, Watertown, Massachusetts 02472. E-mail: vkupelian@neriscience.

Address all reprint requests to: John B. McKinlay, Senior Vice President, New England Research Institutes, 9 Galen Street, Watertown, Massachusetts 02472. E-mail: bach@neriscience.com.

Disclosure statement: V.K., C.L., and J.B. have nothing to declare. R.R. is a consultant to Sanofi-Aventis and Eli Lilly. F.H. is on the Speakers Bureau for Solvay Pharmaceuticals and has received grant support from Solvay Pharmaceuticals for an investigator-initiated study.

This work was supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (National Institutes of Health) DK 56842, and a grant from Solvay Pharmaceuticals.

References

- Ferrannini E, Haffner SM, Mitchell BD, Stern MP 1991 Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia* 34:416–422
- Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM 2003 The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. *Diabetes Care* 26:3153–3159
- Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, Isles C, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J 2003 Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation* 108:414–419
- Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB 2002 Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab* 87:589–598
- Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR 2001 Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab* 86:724–731
- Haffner SM, Shaten J, Stern MP, Smith GD, Kuller L 1996 Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. MRFIT Research Group. Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 143:889–897
- Stellato RK, Feldman HA, Hamdy O, Horton ES, McKinlay JB 2000 Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts Male Aging Study. *Diabetes Care* 23:490–494
- Tsai EC, Matsumoto AM, Fujimoto WY, Boyko EJ 2004 Association of bioavailable, free, and total testosterone with insulin resistance: influence of sex hormone-binding globulin and body fat. *Diabetes Care* 27:861–868
- van den Beld AW, de Jong FH, Grobbee DE, Pols HA, Lamberts SW 2000 Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. *J Clin Endocrinol Metab* 85:3276–3282
- Zmuda JM, Cauley JA, Kriska A, Glynn NW, Gutai JP, Kuller LH 1997 Longitudinal relation between endogenous testosterone and cardiovascular disease risk factors in middle-aged men. A 13-year follow-up of former Multiple Risk Factor Intervention Trial participants. *Am J Epidemiol* 146:609–617
- Barrett-Connor E, Khaw KT 1988 Endogenous sex hormones and cardiovascular disease in men. A prospective population-based study. *Circulation* 78:539–545
- Hak AE, Witteman JC, de Jong FH, Geerlings MI, Hofman A, Pols HA 2002 Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. *J Clin Endocrinol Metab* 87:3632–3639
- Muller M, van der Schouw YT, Thijssen JH, Grobbee DE 2003 Endogenous sex hormones and cardiovascular disease in men. *J Clin Endocrinol Metab* 88:5076–5086
- Oh JY, Barrett-Connor E, Wedick NM, Wingard DL 2002 Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo study. *Diabetes Care* 25:55–60
- Kupelian V, Page ST, Araujo AB, Travison TG, Bremner WJ, McKinlay JB 2006 Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men. *J Clin Endocrinol Metab* 91:843–850
- Kupelian V, Shabsigh R, Araujo AB, O'Donnell AB, McKinlay JB 2006 Erectile dysfunction as a predictor of the metabolic syndrome in aging men: results from the Massachusetts Male Aging Study. *J Urol* 176:222–226
- Laaksonen DE, Niskanen L, Punnonen K, Nyyssönen K, Tuomainen TP, Valkonen VP, Salonen R, Salonen JT 2004 Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care* 27:1036–1041
- Muller M, Grobbee DE, den Tonkelaar I, Lamberts SW, van der Schouw YT 2005 Endogenous sex hormones and metabolic syndrome in aging men. *J Clin Endocrinol Metab* 90:2618–2623
- Rodriguez A, Muller DC, Metter EJ, Maggio M, Harman SM, Blackman MR, Andres R 2007 Aging, androgens, and the metabolic syndrome in a longitudinal study of aging. *J Clin Endocrinol Metab* 92:3568–3572
- McKinlay JB, Link CL 2007 Measuring the urologic iceberg: design and implementation of the Boston Area Community Health (BACH) survey. *Eur Urol* 52:389–396
- Sodergard R, Backstrom T, Shanbhag V, Carstensen H 1982 Calculation of free and bound fractions of testosterone and estradiol-17 β to human plasma proteins at body temperature. *J Steroid Biochem* 16:801–810
- Vermeulen A, Verdonck L, Kaufman JM 1999 A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab* 84:3666–3672
- Alberti KG, Zimmet PZ 1998 Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539–553
- Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults 2001 Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497
- Balkau B, Charles MA 1999 Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). *Diabet Med* 16:442–443
- Einhorn D, Reaven GM, Cobin RH, Ford E, Ganda OP, Handelsman Y, Hellman R, Jellinger PS, Kendall D, Krauss RM, Neufeld ND, Petak SM, Rodbard HW, Seibel JA, Smith DA, Wilson PW 2003 American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract* 9:237–252
- Alberti KG, Zimmet P, Shaw J 2005 The metabolic syndrome: a new worldwide definition. *Lancet* 366:1059–1062
- Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith Jr SC, Spertus JA, Costa F 2005 Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 112:2735–2752
- Schafer J 1997 Analysis of incomplete multivariate data. London: Chapman and Hall
- Cochran W 1977 Sampling Techniques. 3rd ed. New York: John Wiley and Sons
- Litman HJ, Bhasin S, Link CL, Araujo AB, McKinlay JB 2006 Serum androgen levels in black, Hispanic, and white men. *J Clin Endocrinol Metab* 91:4326–4334
- Khaw KT, Barrett-Connor E 1992 Lower endogenous androgens predict central adiposity in men. *Ann Epidemiol* 2:675–682
- Haffner SM, Valdez RA, Mykkanen L, Stern MP, Katz MS 1994 Decreased testosterone and dehydroepiandrosterone sulfate concentrations are associated with increased insulin and glucose concentrations in nondiabetic men. *Metabolism* 43:599–603
- Simon D, Preziosi P, Barrett-Connor E, Roger M, Saint-Paul M, Nahoul K, Papoz L 1992 Interrelation between plasma testosterone and plasma insulin in healthy adult men: the Telecom Study. *Diabetologia* 35:173–177
- Tchernof A, Labrie F, Belanger A, Prud'homme D, Bouchard C, Tremblay A, Nadeau A, Despres JP 1997 Relationships between endogenous steroid hor-

- mon, sex hormone-binding globulin and lipoprotein levels in men: contribution of visceral obesity, insulin levels and other metabolic variables. *Atherosclerosis* 133:235–244
36. **Kaukua J, Pekkarinen T, Sane T, Mustajoki P** 2003 Sex hormones and sexual function in obese men losing weight. *Obes Res* 11:689–694
37. **Niskanen L, Laaksonen DE, Punnonen K, Mustajoki P, Kaukua J, Rissanen A** 2004 Changes in sex hormone-binding globulin and testosterone during weight loss and weight maintenance in abdominally obese men with the metabolic syndrome. *Diabetes Obes Metab* 6:208–215
38. **Page ST, Amory JK, Bowman FD, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL** 2005 Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *J Clin Endocrinol Metab* 90:1502–1510
39. **Saad F, Gooren LJ, Haider A, Yassin A** 2008 A dose-response study of testosterone on sexual dysfunction and features of the metabolic syndrome using testosterone gel and parenteral testosterone undecanoate. *J Androl* 29:102–105
40. **Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, Holmes JH, Dlewati A, Santanna J, Rosen CJ, Strom BL** 1999 Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab* 84:2647–2653
41. **Wang C, Swedloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, Matsumoto AM, Weber T, Berman N** 2000 Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. Testosterone Gel Study Group. *J Clin Endocrinol Metab* 85:2839–2853
42. **Xu X, De Pergola G, Bjorntorp P** 1990 The effects of androgens on the regulation of lipolysis in adipose precursor cells. *Endocrinology* 126:1229–1234
43. **Xu XF, De Pergola G, Bjorntorp P** 1991 Testosterone increases lipolysis and the number of β -adrenoceptors in male rat adipocytes. *Endocrinology* 128:379–382
44. **Marin P, Oden B, Bjorntorp P** 1995 Assimilation and mobilization of triglycerides in subcutaneous abdominal and femoral adipose tissue *in vivo* in men: effects of androgens. *J Clin Endocrinol Metab* 80:239–243
45. **Rebuffe-Scrive M, Marin P, Bjorntorp P** 1991 Effect of testosterone on abdominal adipose tissue in men. *Int J Obes* 15:791–795