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Low Sex Hormone-Binding Globulin, Total Testosterone, and Symptomatic Androgen Deficiency Are Associated with Development of the Metabolic Syndrome in Nonobese Men

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Background: The metabolic syndrome (MetS), characterized by central obesity, lipid and insulin dysregulation, and hypertension, is a precursor state for cardiovascular disease. The purpose of this analysis was to determine whether low serum sex hormone levels or clinical androgen deficiency (AD) predict the development of MetS.

Methods: Data were obtained from the Massachusetts Male Aging Study, a population-based prospective cohort of 1709 men observed at three time points (T_1, 1987–1989; T_2, 1995–1997; T_3, 2002–2004). MetS was defined using a modification of the ATP III guidelines. Clinical AD was defined using a combination of testosterone levels and clinical signs and symptoms. The association between MetS and sex hormone levels or clinical AD was assessed using relative risks (RR), and 95% confidence intervals (95% CI) were estimated using Poisson regression models.

Results: Analysis was conducted in 950 men without MetS at T_1. Lower levels of total testosterone and SHBG were predictive of MetS, particularly among men with a body mass index (BMI) below 25 kg/m^2 with adjusted RRs for a decrease in 1 SD of 1.41 (95% CI, 1.06–1.87) and 1.65 (95% CI, 1.12–2.42). Results were similar for the AD and MetS association, with RRs of 2.51 (95% CI, 1.12–5.65) among men with a BMI less than 25 compared with an RR of 1.22 (95% CI, 0.66–2.24) in men with a BMI of 25 or greater.

Conclusions: Low serum SHBG, low total testosterone, and clinical AD are associated with increased risk of developing MetS over time, particularly in nonoverweight, middle-aged men (BMI, <25). Together, these results suggest that low SHBG and/or AD may provide early warning signs for cardiovascular risk and an opportunity for early intervention in nonobese men. **(*J Clin Endocrinol Metab* 91: 843–850, 2006)**

CORONARY ARTERY DISEASE (CAD) and type 2 diabetes mellitus (DM) are major causes of morbidity and mortality in the United States, with prevalence rates of 6.9% and 6.7%, respectively, and with CAD causing one of every five deaths (1). Unfortunately, by the time these chronic diseases present clinically, irreversible vascular damage has already occurred. It is estimated that type 2 DM is diagnosed, on the average, 4–7 yr after onset (2). To best target prevention strategies, it is critical to identify upstream determinants of disease. The metabolic syndrome (MetS), which incorporates criteria of dyslipidemia, hyperglycemia, hypertension, and central adiposity, has been established as a precursor state in which patients meeting the criteria for MetS clearly are at significantly increased risk of developing CAD and DM (3, 4). However, less is known about determinants further upstream; that is, the predictors of developing MetS need to be identified.

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Abbreviations: AD, Androgen deficiency; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; HDL, high-density lipoprotein; MetS, metabolic syndrome; RR, relative risk; T, testosterone; T_1, baseline; T_2, first follow-up; T_3, second follow-up.

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In men, aging is associated with a gradual decline in testosterone (T) (5, 6). This decrease accompanies changes in body composition, including increases in fat mass and decreases in lean body mass (7), disorders of insulin and glucose metabolism (8–10), and dyslipidemia (8, 11). The relationship among T, cardiovascular disease, and diabetes is poorly understood (12). Small intervention trials have demonstrated that exogenous T supplementation in young men lowers high-density lipoprotein (HDL) (13, 14). In contrast, T replacement in older men with low serum T compared with young healthy men, increases lean body mass and decreases fat mass, total cholesterol, and low-density lipoprotein without affecting HDL, all of which may be associated with decreased risk of CVD (15, 16). Moreover, T may have more direct effects on vascular reactivity and cardiac muscle (17, 18). More recently, low serum T and SHBG levels have been directly associated with the MetS, both cross-sectionally (19) and longitudinally (20).

The definition of androgen deficiency (AD) is still a matter of controversy. AD can be defined purely biochemically, using T levels with percentile cutoff values (*e.g.* 2.5 SD below the range for normal young males), (6) or using only signs and symptoms (21). The problem with the first method is that not all individuals with relatively low T levels are symptomatic. In contrast, symptom questionnaires tend to have low specificity due to the nonspecific nature of the signs and

symptoms evaluated by these screening tools (21). A diagnostic algorithm outlined at The Endocrine Society meeting in 2001 was the basis for an alternative operational definition of AD combining both clinical signs and symptoms and measurements of total T and calculated free T (22, 23).

The purpose of these analyses was to determine the relationship between sex hormones or AD and subsequent development of MetS. Data were obtained from the Massachusetts Male Aging Study (MMAS), a large prospective cohort of men aged between 40 and 70 yr at baseline who have been followed for more than 15 yr.

Subjects and Methods

The MMAS is a population-based observational cohort study of aging men observed at three time points: baseline (T_1), 1987–1989; first follow-up (T_2), 1995–1997; and second follow-up (T_3), 2002–2204. The sampling design and field protocol were described previously (24). Briefly, men aged 40–70 yr were randomly selected from 11 cities and towns in the Boston, Massachusetts, area. Men in older age groups were oversampled to provide approximately equal proportions in each decade (40–49, 50–59, and 60–70 yr). At baseline (T_1), a total of 1709 men (response rate, 52%) were enrolled in the study. A telephone survey of nonrespondents (n = 206) revealed that they were similar to respondents in general health and prevalence of chronic diseases. At the first follow-up phase (T_2), 1496 of the original 1709 men were eligible, and 1156 completed a T_2 interview (response rate, 77%). At the second follow-up phase (T_3), 1351 men were eligible, of whom 853 were interviewed (response rate, 63%). Median follow-up was 14.4 yr (range, 7.1–16.9 yr).

The sample used for this analysis was obtained as follows. Men not followed at both T_2 and T_3 were excluded (495 men). An additional 146 men with MetS at baseline were excluded. Finally, 118 men were excluded because of missing data on hormone levels, AD, or potential covariates. The final analysis for this study was conducted on 950 men.

Data collection and measures used

The field protocol for MMAS has been previously described (24). Briefly, a trained field technician/phlebotomist visited each subject in his home and administered a health questionnaire and psychological assessment. Anthropometric data on height, weight, and waist and hip circumferences were obtained using standardized procedures developed for large-scale epidemiological field studies (25). Blood pressure (BP) measurements while the subject was seated were obtained at two points, 25 min apart, during the interview and were averaged. The presence of medical conditions, including diabetes and heart disease, was assessed through self-report. Current prescriptions and nonprescription medications and clinical indication for each were assessed by the field technician. Medications were then coded according to the American Hospital Formulary Service classification (26). MMAS received institutional review board approval, and all participants gave written informed consent.

MetS definition

The MetS was first operationally defined by a World Health Organization Consultant Group (27) and subsequently refined by a National Institutes of Health Expert Panel (referred to as the ATP III guidelines) (28). Available MMAS data permit close adherence to the current ATP III guidelines with the major exception that only nonfasting blood samples were available for analyses, impacting analyses of triglycerides and fasting glucose. Therefore, for the purposes of this analysis, MetS was defined as presence of three or more of the following: 1) waist larger than 40 in.; 2) systolic BP greater than 130 mm Hg, diastolic BP greater than 85 mm Hg, or antihypertensive medication use; 3) HDL cholesterol less than 40 mg/dl or lipid medication use; 4) self-reported diabetes; and 5) triglycerides greater than 150 mg/dl (not available at baseline).

Hormone measurements

Nonfasting blood samples were drawn within 4 h of the subject's awakening to control for diurnal variation in hormone levels. Two samples were drawn 30 min apart and pooled for analysis to control for episodic secretion (29). Blood was kept in an ice-cooled container for transport and was centrifuged within 6 h. Serum was stored in 5-ml scintillation vials at −20 C, shipped to the laboratory within 1 wk by same-day courier, and stored at −70 C until assay. All hormone measurements were performed at the Endocrine Laboratory of University of Massachusetts Medical Center (Worcester, MA). Total T and SHBG were measured by RIA [Diagnostic Products Corp. (Los Angeles, CA) for total T; Farmos kit for SHBG]. Intraassay coefficients of variation for these assays were 5.4% and 5.0% respectively. Interassay coefficients of variation were 8.0% and 6.0%. Free T was calculated from total T and SHBG measurements using Vermeulen's method (31).

Definition of AD

An operational definition of AD, based on a diagnostic algorithm presented at the Second Annual Andropause Consensus Meeting (22) and available MMAS data, was constructed. Methods similar to the algorithm proposed by the consensus statement have been reported (30, 31). A detailed description and discussion of this method were published previously (23). Briefly, of the 12 signs/symptoms identified at the consensus meeting, data for eight were available in the MMAS study: loss of libido, depression (defined as current use of antidepressant medication), erectile dysfunction, lethargy, inability to concentrate, sleep disturbance, irritability, and depressed mood. Men were classified as having AD if they met one of the following conditions: 1) at least three signs/symptoms and total T less than 200 ng/dl (6.94 nmol/liter); and 2) at least three signs/symptoms and total T of 200–400 ng/dl (6.94–13.88 nmol/liter) and free T less than 8.91 ng/dl (0.3092 nmol/liter).

Statistical analysis

Descriptive statistics, proportions for categorical variables, and means and SDs for continuous variables were used to describe the baseline total sample (n = 1709) and the analytic sample (n = 950). The purpose of the analysis was to determine whether sex hormone levels or AD at baseline were predictors for incident MetS at T_2 or T_3. Person-years accumulated from T_1 to the year of event or the last contact. Relative risks (RR) and 95% confidence intervals (95% CI) were used to assess the magnitude of the association between hormone levels (total T, free T, and SHBG) or AD and MetS. For hormone levels, RRs were reported per decrease in 1 SD and for quartiles of the hormone distributions. Multiple regression models, estimated using Poisson regression, were used to adjust for potential confounders. The use of Poisson regression is appropriate in cohort studies where rates and rate ratios for a specified time period are of interest (32). Baseline measures adjusted for in the analysis as potential confounders include age (grouped as 40–49, 50–59, and ≥60 yr of age), body mass index (BMI; categorized as <25, 25–29.9, and ≥30 kg/m^2 according to the National Center for Health Statistics definitions for overweight or obese) (33) smoking at baseline (defined as smoking cigarettes, cigars, cigarillos, or pipe) *vs.* nonsmokers, and subjects' self-reported health (defined as excellent, very good, good, or fair/poor). A variable, MSscore, was used to indicate the number of conditions within MetS (*e.g.* high blood pressure or waist >40 in.) present at T_1 (zero, one, or two) in subjects who did not meet the full criteria for MetS at baseline and were included in the analysis. Likelihood ratio tests were used to assess the contributions of confounders and interaction terms to the model. Interaction assessment was performed by looking at the difference in magnitude in RRs across strata if the *P* value from the likelihood ratio test was less than 0.2. All reported RRs and 95% CIs were estimated using Poisson regression. All analyses were conducted using the commercial statistical package Stata 7.0 (Stata Corp., College Station, TX).

Results

Baseline characteristics of the MMAS sample and the analytic sample are presented in Table 1. The cohort was predominantly white, and a majority had been educated beyond high school. Only 5% of the men (n = 49) in the analytic sample had AD at T_1. In the analytic sample, most men

TABLE 1. T_1 characteristics of the full and analytic study samples

Baseline characteristic	T_1 (n = 1709)		MetS at T_1 (n = 146)		Analytic sample (n = 950)	
	n	%	n	%	n	%
Age mean (SD)	54.7	(8.7)	56.5	(8.0)	52.9	(8.3)
Age groups (10-yr)						
40–49	566	33	31	21	382	40
50–59	564	33	57	39	329	35
60–70	579	34	58	40	239	25
Race						
White	1629	95	141	97	922	97
Black	52	3	31	2	16	2
Other	25	1	2	1	10	1
Education						
High school or less	488	29	51	35	210	22
Some college or BA	707	41	69	47	376	40
Advanced study beyond BA	513	30	26	18	364	38
MetS cases	262	15	146	100%	0	0
Androgen deficiency[a]	107	6	13	8.9	49	5
BMI mean (SD)	27.3	(4.4)	32.3	(5.5)	26.3	(3.4)
BMI groups						
<25	509	30	3	2	344	36
≥25	1199	70	143	98	606	64
Self-reported health						
Excellent	529	31	36	14	353	37
Very good	603	35	78	32	371	39
Good	434	25	96	39	188	20
Fair/poor	141	8	38	15	38	4
Currently smoking	552	32	77	31	293	31
BP						
Systolic mean (SD)	126.9	(16.2)	136.9	(12.6)	124.3	(14.1)
Diastolic mean (SD)	79.8	9.5	84.9	(9.3)	79.1	(8.4)
BP medication use	276	16	54	37	84	9
High BP (>130/85 or BP med)	844	49	141	97	373	39
Waist circumference mean (SD)	38.4	(4.6)	44.1	(3.8)	37.2	(3.7)
Waist circumference >40 in.	513	30	140	96	166	17
HDL-C mean (SD)	42.6	(18.7)	32.7	(6.4)	44.6	(13.2)
HDL-C <40	791	48	135	92	355	37
Lipid medication use	23	1	4	3	6	1
Diabetes	131	8	33	23	21	2
Total T (nmol/liter)	17.9	(17.9)	15.6	(6.4)	18.4	(5.9)
SHBG (nmol/liter)	32.2	(16.2)	26.1	(11.8)	33.6	(16.1)
Free T (nmol/liter)	0.46	(0.18)	0.43	(0.19)	0.47	(0.18)

[a] Adopted from the Second Annual Andropause Consensus Meeting; see *Subjects and Methods*.

reported overall good health, with only 4% reporting fair or poor health. Approximately 30% were current smokers. Over 60% had a BMI of 25 or larger. Conversely, only 17% had a waist circumference greater than 40 in. Thirty-eight percent reported elevated blood pressure.

Men included in the final analysis sample were slightly younger than the total initial cohort. They also tended to have slightly lower BMI, waist circumference, and blood pressure; reported excellent and very good health more often; and had slightly higher HDL cholesterol concentrations. This was expected, because cases of MetS were excluded at baseline, and men who were deceased or seriously ill were not followed. Forty percent of men in the analysis sample were 40–49 yr old compared with 33% in the total sample.

The occurrence of MetS by baseline risk factors is presented in Table 2. Overall, 300 new cases of MetS were reported at T_2 and T_3. The overall incidence was 25.5/1000 person-years. Age at baseline was not associated with incidence of MetS. Smoking was associated with a moderate increase in risk of MetS with a RR of 1.50 (95% CI, 1.19–1.89). Worse self-reported health was predictive of development of MetS, with the RR increasing from 1.28 (95% CI, 0.97–1.68) for very good health to 2.15 (95% CI, 1.33–3.49) for fair/poor health, with excellent health as the reference category. As expected, BMI and the number of conditions defining MetS at baseline were strong predictors of development of MetS.

Associations of MetS with hormone levels (total T, free T, and SHBG) at baseline are presented in Table 3. There was an overall trend of increasing risk of MetS with decreasing levels of both total T and SHBG [unadjusted RRs for a decrease in 1 SD were 1.17 (95% CI, 1.04–1.32) and 1.39 (95% CI,1.20–1.61), respectively], but there was no association between free T and MetS (RR, 0.97; 95% CI, 0.87–1.08). Compared with the highest quartile (>75%) of the distributions, the risk of MetS was higher for lower quartiles of total T and SHBG, but not for free T. The increase in risk was more linear for SHBG [RR, 1.69 (95% CI, 1.15–2.46), 1.84 (95% CI, 1.26–2.59), and 2.35 (95% CI, 1.56–3.17) for the lower quartiles] than for total T [RR, 1.18 (95% CI, 0.84–1.67), 1.60 (95% CI, 1.15–2.21), and 1.43 (95% CI, 1.03–2.00)]. Adjusting for potential confounders, the magnitude of the RRs was attenuated, but the overall trends remained the same. The association of both total T and SHBG with MetS seemed to be modified by BMI, with stronger associations observed

TABLE 2. Association of T_1 (1987–1989) measures withMetS at follow-up T_2 (1995–1997) or T_3 (2002–2004)

	n	MetS	Person-years	IR per 1000py[a]	RR (95% CI)
Age (yr)					
40–49	382	117	4824	24.3	1.00
50–59	329	115	4084	28.2	1.16 (0.90–1.50)
60–69	239	68	2838	24	0.99 (0.73–1.33)
BMI, continuous					1.13 (1.10–1.16)
BMI					
<25	344	47	4470	10.5	1.00
25–29.9	488	189	5955	31.7	3.02 (2.19–4.15)
≥30	118	64	1320	48.5	4.61 (3.17–6.72)
Smoking					
No	657	184	8265	22.3	1.00
Yes	293	116	3479	33.3	1.50 (1.19–1.89)
MSscore[b]					
0	298	45	3974	11.3	1.00
1	389	116	4826	24	2.12 (1.50–3.00)
2	263	139	2945	47.2	4.17 (2.98–5.83)
Self-reported health					
Excellent	353	91	4537	20.1	1.00
Very good	371	116	4535	25.6	1.28 (0.97–1.68)
Good	188	73	2210	33	1.65 (1.21–2.24)
Fair/poor	38	20	463	43.2	2.15 (1.33–3.49)

[a] IR per 1000py, Incidence rates per 1000 person-years.
[b] Number of conditions part of the MetS definition (high blood pressure, self-reported diabetes, HDL < 40 mg/dl, waist > 40 in.).

among men with BMI below 25 (Table 4). Adjusted RRs per decrease in 1 SD were 1.41 (95% CI, 1.06–1.87) for total T and 1.65 (95% CI, 1.12–2.42) for SHBG among men with BMI below 25 compared with RRs of 1.07 (95% CI, 0.93–1.23) and 1.13 (95% CI, 0.96–1.32) among men with BMI of 25 or more. Similarly, adjusted RRs for lower quartiles compared with the highest quartile ranged between 1.40 (95% CI, 0.55–3.56) and 2.64 (95% CI, 1.10–6.32) for total T and between 2.89 (95% CI, 0.94–8.87) and 4.65 (95% CI, 1.73–12.48) for SHBG among men with BMI below 25, whereas among men with BMI of 25 or more, adjusted RRs ranged between 1.04 (95% CI, 0.71–1.51) and 1.25 (95% CI, 0.87–1.78) for total T and between 1.10 (95% CI, 0.72–1.66) and 1.35 (95% CI, 0.92–1.98) for SHBG. There was no interaction between free T and BMI.

Analyses were repeated using the operational definition of AD (Table 5). There was no overall association between AD and MetS (RR, 1.19; 95% CI, 0.74–1.92). As with total T and SHBG, there was a stronger association between AD and MetS among men with BMI less than 25 (RR, 2.62; 95% CI, 1.17–5.84) than among men with BMI of 25 or more. This effect did not change after adjusting for additional potential confounders (MSscore, age, smoking, and self-reported health). The adjusted RRs for AD were 2.51 (95% CI, 1.12–

TABLE 3. Association of total T, free T, and SHBG at baseline T_1 (1987–1989) with incident MetS at follow-up T_2 (1995–1997) or T_3 (2002–2004)

	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[a]
Total T (nmol/liter), SD = 5.9		
Decrease 1 SD	1.17 (1.04–1.32)	1.13 (0.99–1.28)
Quartiles		
>75% (21.8–46.9)	1.00	1.00
50–75% (17.9–21.7)	1.18 (0.84–1.67)	1.09 (0.77–1.55)
25–50% (14.5–17.8)	1.60 (1.15–2.21)	1.40 (1.01–1.95)
<25% (1.2–14.4)	1.43 (1.03–2.00)	1.30 (0.93–1.82)
SHBG (nmol/liter), SD = 16		
Decrease 1 SD	1.39 (1.20–1.61)	1.20 (1.03–1.40)
Quartiles		
>75% (40–170)	1.00	1.00
50–75% (30–39)	1.69 (1.15–2.46)	1.35 (0.92–1.98)
25–50% (23–29)	1.80 (1.26–2.59)	1.48 (1.02–2.14)
<25% (6–22)	2.22 (1.56–3.17)	1.57 (1.08–2.27)
Free T (nmol/liter), SD = 0.18		
Decrease 1 SD	0.97 (0.87–1.08)	1.01 (0.89–1.14)
Quartiles		
>75% (0.57–1.36)	1.00	1.00
50–75% (0.46–0.57)	1.13 (0.83–1.54)	1.07 (0.78–1.46)
25–50% (0.34 –0.45)	0.93 (0.67–1.28)	0.85 (0.61–1.19)
<25% (0.03 - .34)	0.93 (0.67–1.28)	1.10 (0.79–1.54)

[a] Adjusted for age, BMI, MSscore [number of conditions part of the MetS definition (high blood pressure, self-reported diabetes, HDL< 40 mg/dl, waist > 40 in.), smoking, self-reported health].

TABLE 4. Association of total T, free T, and SHBG at baseline T_1 (1987–1989) with incident MetS at follow-up T_2 (1995–1997) or T_3 (2002–2004) by baseline BMI levels

	BMI	RR (95% CI)	Adjusted RR (95% CI)[a]
Total T (nmol/liter), SD = 5.9			
Decrease 1 SD	<25	1.40 (1.06–1.86)	1.41 (1.06–1.87)
Decrease 1 SD	≥25	1.04 (0.91–1.20)	1.07 (0.93–1.23)
	P value[b]	0.062	0.079
Quartiles of total T			
>75% (21.8–46.9)	<25	1.00	1.00
50–75% (17.9–21.7)		1.49 (0.59–3.78)	1.40 (0.55–3.56)
25–50% (14.5–17.8)		2.69 (1.14–6.35)	2.59 (1.09–6.11)
<25% (1.2–14.4)		2.57 (1.08–6.12)	2.64 (1.10–6.32)
>75% (21.8–46.9)	≥25	1.00	1.00
50–75% (17.9–21.7)		1.05 (0.72–1.53)	1.04 (0.71–1.51)
25–50% (14.5–17.8)		1.26 (0.89–1.80)	1.25 (0.87–1.78)
<25% (1.2–14.4)		1.10 (0.77–1.59)	1.14 (0.79–1.64)
	P value[b]	0.242	0.240
SHBG (nmol/liter), SD = 16			
Decrease 1 SD	<25	1.72 (1.18–2.51)	1.65 (1.12–2.42)
Decrease 1 SD	≥25	1.17 (1.01–1.37)	1.13 (0.96–1.32)
	P value[b]	0.056	0.060
Quartiles of SHBG			
>75% (40–170)	<25	1.00	1.00
50–75% (30–39)		3.92 (1.43–10.80)	3.49 (1.27–9.64)
25–50% (23–29)		5.04 (1.88–13.50)	4.65 (1.73–12.48)
<25% (6–22)		3.15 (1.03–9.63)	2.89 (0.94–8.87)
>75% (40–170)	≥25	1.00	1.00
50–75% (30–39)		1.27 (0.84–1.91)	1.10 (0.72–1.66)
25–50% (23–29)		1.20 (0.81–1.78)	1.15 (0.77–1.72)
<25% (6–22)		1.51 (1.04–2.20)	1.35 (0.92–1.98)
	P value[b]	0.030	0.037
Free T (nmol/liter), SD = 0.18			
Decrease 1 SD	<25	1.06 (0.81–1.39)	1.10 (0.84–1.45)
Decrease 1 SD	≥25	0.95 (0.84–1.08)	0.99 (0.86–1.12)
	P value[b]	0.469	0.461
Quartiles of free T			
>75% (0.57 - 1.36)	<25	1.00	1.00
50–75% (0.46 - 0.57)		1.12 (0.48–2.59)	1.06 (0.46–2.47)
25–50% (0.34 - 0.45)		1.01 (0.41–2.50)	1.03 (0.42–2.54)
<25% (0.03 - 0.34)		1.41 (0.64–3.11)	1.55 (0.70–3.44)
>75% (0.57 - 1.36)	≥25	1.00	1.00
50–75% (0.46 - 0.57)		1.17 (0.84–1.63)	1.07 (0.77–1.50)
25–50% (0.34 - 0.45)		0.88 (0.62–1.24)	0.82 (0.58–1.18)
<25% (0.03 - 0.34)		0.90 (0.63–1.29)	1.02 (0.70–1.48)
	P value[b]	0.650	0.724

[a] Adjusted for age, BMI, MSscore [number of conditions part of the MetS definition (high blood pressure, self-reported diabetes, HDL < 40 mg/dl, waist > 40 in.), smoking, self-reported health].
[b] Likelihood-ratio test comparing models with and without the interaction term.

5.65) when BMI was less than 25 and 1.22 (95% CI, 0.66–2.24) when BMI was 25 or greater.

Discussion

In a population-based cohort of 950 randomly selected, middle-aged men, total T and SHBG levels were associated with the development of MetS. Among nonoverweight men, lower quartiles of total T and SHBG, compared with the highest quartile, showed a 2- to 4-fold increase in risk of developing MetS. Similarly, a 2-fold increase in the risk of MetS was observed among men with both clinical and biochemical AD and BMI less than 25. These relationships were independent of age, smoking, self-reported overall health status, and number of conditions defining MetS. We observed an overall trend of increasing MetS risk with lower total T levels and SHBG levels, but there was no clear threshold effect.

Our results are consistent with other recent studies. Using a cross-sectional study, Muller *et al.* (19) found a decrease in the risk of MetS with increasing levels of total T and SHBG independent of age, smoking, alcohol consumption, physical activity, and BMI (19). Using a longitudinal approach, Laaksonen *et al.* (20) showed a 2-fold increase in the risk of MetS for the lowest quartile of T compared with the highest, independently of potential confounders, such as CAD, smoking, alcohol consumption, and socioeconomic status (20). Low levels of endogenous sex hormones have also been associated with risk factors for MetS, such as increased central adiposity (19, 34) and insulin resistance (35, 36). Similarly, low total T and SHBG levels have been associated with unfavorable lipid profiles, including increased triglyceride, total cholesterol, and low-density lipoprotein concentrations (37) and decreased HDL levels (11). We did not find the relationship between free T and MetS reported by others (20), suggesting that the impact of total T on MetS risk is mediated through SHBG. Finally, our observation that the risk of MetS

TABLE 5. Association of AD at T_1 (1987–1989) with incident MetS at follow-up T_2 (1995–1997) or T_3 (2002–2004), overall and by baseline BMI levels

BMI	AD	MetS	Person-years	IR per 1000py[a]	RR (95% CI)	
					Unadjusted	Adjusted for age, BMI, MSscore,[b] smoking, self-reported health
	No	282	11149	25.3	1.00	1.00
	Yes	18	596	30.2	1.19 (0.74–1.92)	1.51 (0.93–2.45)
<25	No	40	4190	9.5	1.00	1.00
	Yes	7	280	25	2.62 (1.17–5.84)	2.51 (1.12–5.65)
≥25	No	242	6959	34.8	1.00	1.00
	Yes	11	316	34.9	1.00 (0.55–1.83)	1.22 (0.66–2.24)
P value[c]					0.082	0.172

[a] IR per 1000py, Incidence rates per 1000 person-years.
[b] Number of conditions part of the MetS definition (high blood pressure, self-reported diabetes, HDL < 40 mg/dl, waist > 40 in.).
[c] Likelihood-ratio test comparing models with and without the interaction term.

with lower levels of total T or SHBG was substantially higher in men with a low-normal BMI (BMI, <25) suggests that the impact of SHBG or total T on MetS risk is overshadowed by the increased risk of MetS associated with adiposity in more obese men.

The mechanism by which higher levels of SHBG might protect against the development of MetS is unclear. How SHBG and MetS are related is not known; however, it is likely that the increased risk for MetS observed in lean men with lower SHBG levels marks a group with higher insulin levels. This increased insulin resistance would predict increased frequency to develop MetS over time. *In vitro* studies in human hepatoma cell lines (HepG2) have demonstrated decreased SHBG production in the setting of insulin (38, 39). *In vivo* diazoxide treatment, resulting in decreased insulin levels, produces a significant increase in SHBG (40), whereas SHBG levels decrease acutely during hyperinsulinemic euglycemic clamp studies (41). Together, these intervention studies suggest that insulin negatively regulates hepatic production of SHBG. In support of this, multiple cross-sectional population studies have demonstrated a negative correlation between SHBG and the development of type 2 diabetes (9, 10, 42); thus, it has been suggested that SHBG may, in fact, act as a surrogate marker for insulin resistance (43, 44).

Our analyses do have a number of limitations, which may explain the discrepancies between our results and others. First, MetS could not be assessed exactly according to the ATP III guidelines, because fasting insulin, glucose, and triglycerides measurements were not available in our dataset. In addition, triglyceride measurements were not available at baseline; thus, MetS assessment was based on only four criteria at that time point. This could result in underestimating the identified new cases of MetS, because some men may have been misclassified as not having MetS at baseline. In addition, using self-reported diabetes to define incident MetS at T_2 and T_3, rather than fasting glucose above 110 mg/dl probably underestimates the number of men who developed MetS during follow-up, resulting in a bias to the null. Despite the recognized limitation, the approach used in this paper has scientific merit because 1) the ATP III components have always only 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; and 3) it is employed as a concept for purposes of epidemiological analysis rather than for clinical purposes. The advantages of the present analysis, cost efficiently using the large already collected MMAS database, clearly outweigh the recognized limitations associated with the measurement of some components.

Our operational definition of clinical AD is not without flaws. The Endocrine Society algorithm calls for the repeat of T measurement when levels are found to be in the intermediate range (200–400 ng/dl). This is clearly not feasible in an observational survey. Unfortunately, the extent and direction of misclassification of men as androgen deficient (and, likewise, not androgen deficient) due to random variability in T levels cannot be known with currently available data. We do not know how T values vary from day to day.

Another possible limitation is the differences between the analysis sample and the original baseline sample, which may affect the generalizability of the results. Given the nature of the questions we sought to answer, it was necessary to define a healthy baseline cohort to establish clearly the temporal sequence between AD and development of MetS. Most exclusions were due to the presence of MetS at baseline and the absence of follow-up. Few men were excluded because of missing information and, as such, are unlikely to affect the results substantially. With regard to generalizability, the MMAS cohort is mostly white and includes men with generally higher socioeconomic status, consistent with the racial and socioeconomic composition of Massachusetts males, aged 40–70 yr at the time of the survey. Longitudinal analyses of the effects of sex steroids on the development of MetS in a more racially diverse group in which the incidence rates of MetS are higher will be an important area of future study.

A final limitation is the small number of MetS cases encountered in some of the categories when assessing the interaction between BMI and quartiles of hormone concentrations or AD, limiting the power to detect statistically significant differences. However, it may be argued that the discrepancy in the magnitude of the association at each level of BMI is more important than the significance of *P* values (45). When using quartiles of both total T and SHBG, the difference between RRs at different BMI levels were substantial and consistent with the interaction effects observed when using these measures as continuous variables, where the limitation of small number did not apply. Similarly, the difference in the magnitude of the association between AD and MetS was substantially higher among men with AD (adjusted RR, 2.51) than among men with BMI greater than

25 (adjusted RR, 1.22), a difference difficult to dismiss based exclusively on the *P* value for the interaction term.

There are many strengths to this study. These include most notably the use of a random, population-based sample of men from a defined geographic area, with the advantage of results generalizable to the underlying population. In addition, the longitudinal design of the study allows the temporal sequence among declining sex steroids, AD, and MetS to be clearly examined. Finally, the use of an operational definition of AD has identified individuals seeking clinical care for clinical symptoms of AD who are at risk for other, more morbid, conditions.

In summary, low levels of total T or SHBG are predictive of MetS, with a stronger association observed with SHBG. These results are consistent with previous findings in the literature. We found that the associations between total T, SHBG, and MetS were significantly stronger among men with BMI below 25. Nonobese men with low SHBG or low total T were at 2- to 4-fold increased risk of developing MetS over 15 yr of follow-up. Similarly, AD, defined using a combination of biochemical measures and clinical signs and symptoms, was predictive of MetS, but only among men with BMI less than 25. The fact that we did not find an increased risk of MetS with low SHBG or total T in men with a BMI of 25 or greater suggests that in overweight and obese men, adiposity is the dominant risk factor for developing MetS and supports a role for exercise and weight loss, rather than androgen therapy, to prevent the development of MetS. Low SHBG, total T, or AD may be early markers of MetS in nonobese men, providing a warning sign in men otherwise considered at lower risk of developing MetS and subsequent diabetes or cardiovascular disease.

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