

# Aging, Androgens, and the Metabolic Syndrome in a Longitudinal Study of Aging

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**Background:** Based on Adult Treatment Panel III criteria, we previously reported that the prevalence of the metabolic syndrome (MS) increased with aging; was higher if elevated 2-h plasma postglucose challenge values were included as a criterion; and was greater in men, compared with women. The aim of this study was to evaluate the relationship between the MS and circulating androgen levels in a cohort of men in the Baltimore Longitudinal Study of Aging.

**Methods and Results:** Study participants were Caucasian community-dwelling adult men in the Baltimore Longitudinal Study of Aging, who underwent a fasting 2-h oral glucose tolerance test and had serum concentrations of total testosterone (T), dehydroepiandrosterone sulfate, and SHBG levels measured. The prevalence of the MS was 4, 21, 21, and 18% for men between the ages of 20 and 39, 40 and

59, 60 and 79, and 80 and 94 yr, respectively. Total T and SHBG were inversely related to the development of the MS over a mean follow-up period of 5.8 yr (range 1.5–14.0 yr), whereas the free T index and body mass index were positively related to the incidence of the MS. Age alone did not predict the development of the MS, nor did the inclusion of abnormal 2-h plasma postglucose challenge levels in the classification of the MS. Stepwise proportional hazards regression analyses showed that among the various measurements, SHBG levels exerted the greatest influence on development of the MS.

**Conclusion:** The prevalence of the MS increased with aging, and this was associated with lower androgen levels. Lower total T and SHBG predicted a higher incidence of the MS. (*J Clin Endocrinol Metab* 92: 3568–3572, 2007)

THE CURRENT ADULT Treatment Panel (ATP) III guidelines define the metabolic syndrome (MS) as the presence of three of five determinants [abdominal adiposity, hypertension, low high-density lipoprotein-cholesterol, elevated triglyceride levels, and abnormal fasting plasma glucose (FPG)] (1). We previously reported that the addition of elevated 2-h plasma postglucose challenge levels (2hPG) as a criterion significantly increased the prevalence of the MS in a cohort of community dwelling Caucasian adult participants in the Baltimore Longitudinal Study of Aging (BLSA) (2). Our results showed that the prevalence of the MS was higher in men, compared with women, which may be related to differences in androgenic effects.

Stellato *et al.* (3) reported that lower total testosterone (T) and SHBG levels predicted subsequent development of type 2 diabetes mellitus (T2DM). These investigators examined the association between low total T and development of T2DM in men between the ages of 40 and 70 yr in the Massachusetts Male Aging Study over a mean follow-up period of approximately 9 yr. Their results

showed that baseline total T and SHBG were significantly lower in men who subsequently developed T2DM.

More recently Laaksonen *et al.* (4) reported that total T and SHBG predicted the development of the MS and T2DM in middle-aged men. These investigators prospectively studied the effects of baseline androgens on the development of the MS in male participants in the Kuopio Ischemic Heart Disease Risk Factor Study who were between 42 and 60 yr of age, after a mean follow-up of approximately 11 yr. Not surprisingly, men who developed the MS showed higher levels of the specific determinants of the MS (higher FPG and waist circumference, more hypertension and dyslipidemia), compared with men without the MS. These investigators also reported that baseline androgen levels were inversely correlated with development of the MS.

The goals of the current study were to determine the relationship between the prevalence of the MS and circulating androgen levels and determine whether baseline androgen levels predicted development of the MS in men in the BLSA. We found that men with the MS had significantly lower levels of T and SHBG. Moreover, baseline total T and SHBG were negatively related to development of the MS, whereas the free testosterone index (FTI) was positively related and dehydroepiandrosterone sulfate (DHEAS) had no effect.

## Subjects and Methods

### Study subjects

Community-dwelling healthy adult men were recruited as participants in the BLSA (5). They were middle- and upper-middle socioeco-

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Abbreviations: ATP, Adult Treatment Panel; BLSA, Baltimore Longitudinal Study of Aging; BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; DM, diabetes mellitus; FPG, fasting plasma glucose; FTI, free testosterone index; 2hPG, 2-h plasma postglucose challenge; MS, metabolic syndrome; OGTT, oral glucose tolerance test; T, testosterone; T2DM, type 2 diabetes mellitus.

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nomic class volunteers, and those included in this analysis were 23–94 yr old. These subjects had longitudinal androgen levels measured from selected BLSA visits starting in the 1960s (6). A baseline visit was defined for this analysis between April 1984 and May 1995 when all measurements were available for the diagnosis of the MS. Of the 912 men who visited the Gerontology Research Center of the National Institute of Aging between these dates, 674 men had all the requisite measurements. Other exclusions included men taking lipid-lowering medications ( $n = 7$ ) and non-Caucasian ethnicity ( $n = 49$ ). This left a final baseline population of 618 men. The BLSA is an ongoing prospective population-based study that was approved by the Institutional Review Board of Johns Hopkins Bayview Medical Center.

### Clinical examination

Data were collected at 0800–0900 h after an overnight fast; subjects wore a light hospital gown, were not permitted to smoke, and were at rest during the oral glucose tolerance test (OGTT). Anthropometric measurements including height, weight, waist circumference, and blood pressure were recorded (7). Fasting plasma glucose levels were obtained, an OGTT was administered to subjects not known to have diabetes, and 2hPG levels were measured (8, 9). MS classification included the following: based on ATPIII, subjects were classified with the MS if there were three of the five determinants present (1); thus, some subjects classified with the MS had a normal FPG.

### Analytical procedures

The glucose oxidase method was used to measure plasma glucose levels (ABA 200 ATC Series II biochromatic analyzer 1983–1992; Abbott Spectrum CCX 1992–1999; Abbott Laboratories, Irving, TX). Plasma triglyceride and total cholesterol concentrations were determined by enzymatic method (Abbott Laboratories ABA-200 ATC biochromatic analyzer). High-density lipoprotein-cholesterol was determined by the dextran sulfate-magnesium precipitation procedure (10). Low-density lipoprotein-cholesterol concentrations were estimated by the Friedewald formula (11). T was determined using  $^{125}\text{I}$  label double-antibody RIA kits obtained from Diagnostic Systems Laboratories (Webster, TX). SHBG concentrations were measured using RIA kits purchased from Radim (Liege, Belgium), which use  $^{125}\text{I}$ -labeled SHBG and polyethylene glycol-complexed second antibody. Blood levels for T were found to increase in relationship to length of storage, which was found to be due to a date-related assay artifact. A mixed-effects model was used to adjust testosterone for the date effect. The FTI was calculated as the ratio of total T/SHBG. The FTI was found to reasonably approximate calculated free T (12) based on the mass action models suggested by Vermeulen *et al.* (13). Serum levels of DHEAS were measured in duplicate by coated-tube RIA by Covance Laboratories (Vienna, VA) using commercial kits (Diagnostic Systems Laboratories).

### Statistical analysis

All data were analyzed using SAS version 9.1 (SAS Institute Inc., Cary NC). Standard methods were used to compute means and sds. Cox proportional hazards analysis was used to estimate risk of the development of the MS associated with baseline levels of T, SHBG, FTI, and DHEAS entered individually in BLSA men who were free of MS and diabetes mellitus (DM). Separate models were computed based on the inclusion of the 2-h plasma glucose level from the OGTT in the definitions of DM and MS. All hazards models were adjusted for baseline age and body mass index (BMI).  $P < 0.05$  was regarded as statistically significant. In an effort to look at the interrelationship of the androgens in the development of the MS, a variable-selection proportional hazards model building algorithm was used. This algorithm finds the three models with the highest likelihood score ( $\chi^2$ ) statistic for all possible model sizes, from one to five variables. The variables used were age, BMI, T, SHBG, and FTI.

## Results

The characteristics of the study population are shown in Table 1. The mean age of the participants was  $63.3 \pm 17.7$  yr, with a range of 23.8–93.9 yr. The mean androgen levels were

**TABLE 1.** Characteristics of the male cohort of BLSA participants

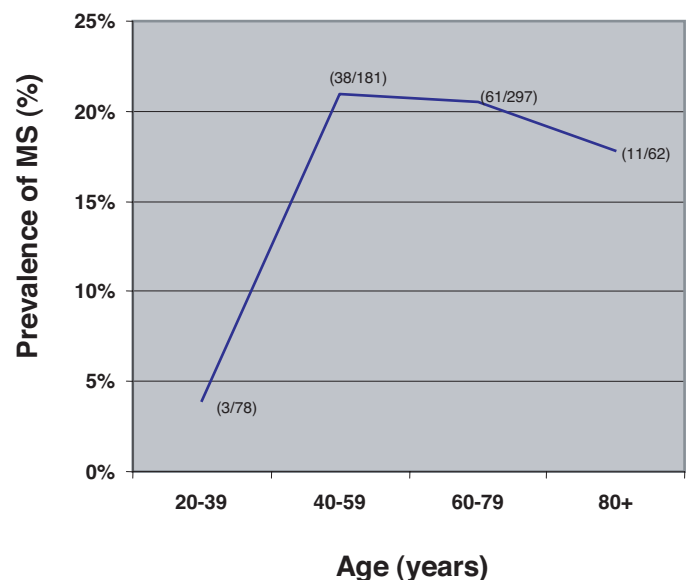
	Mean $\pm$ SD	Range
Age (yr)	$63.3 \pm 17.7$	23.8–93.9
Total T (ng/dl)	$415.9 \pm 98.1$	126.0–765.1
FTI	$5.8 \pm 2.9$	–1.1–19.6
SHBG (ng/dl)	$77.5 \pm 37.0$	15.1–264.0
DHEAS (ng/ml) <sup>a</sup>	$1173.0 \pm 794.2$	50–4310
BMI ( $\text{kg}/\text{m}^2$ )	$26.0 \pm 3.7$	18.6–46.4
FPG (mg/dl)	$101.3 \pm 12.8$	69–222
2hPG (mg/dl)	$140.3 \pm 50.1$	46–419
Systolic BP (mm Hg)	$134.3 \pm 20.5$	85–236
Diastolic BP (mm Hg)	$82.6 \pm 10.5$	50–120
HDL-C (mg/dl)	$41.4 \pm 11.1$	10–86
TRIG (mg/dl)	$116.1 \pm 77.4$	18–693
Waist circumference (cm)	$93.6 \pm 10.9$	68–146
WHR	$0.93 \pm 0.06$	0.76–1.38

Values are age-adjusted mean  $\pm$  SD ( $n = 618$ ). BP, Blood pressure; HDL-C, high-density lipoprotein-cholesterol; TRIG, triglycerides; WHR, waist to hip ratio.

<sup>a</sup> DHEAS analysis performed in a subset of participants ( $n = 577$ ).

within the normal range for each measurement, although some individuals were hypogonadal. The mean BMI was  $26.0 \pm 3.7 \text{ kg}/\text{m}^2$ , with a range of 18.6–46.4  $\text{kg}/\text{m}^2$ . The mean values for the five parameters used in the ATPIII criteria of the MS were the following: waist circumference,  $93.6 \pm 10.9$  cm (range 68–146); fasting plasma glucose,  $101.3 \pm 12.8$  mg/dl (range 69–222); hypertension, systolic blood pressure,  $134.4 \pm 20.5$  mm Hg (range 85–236); diastolic blood pressure,  $82.6 \pm 10.5$  mm Hg (range 50–120); triglycerides,  $116.1 \pm 77.4$  mg/dl (range 18–693); and high-density cholesterol,  $41.4 \pm 11.1$  mg/dl (range 10–86). As shown in Fig. 1, the prevalence of the MS increased significantly ( $P < 0.005$ ) with aging.

Androgen and SHBG levels in men with and without the MS across the different age groups are shown in Fig. 2. The age-adjusted levels of total T ( $368.7 \pm 6.2$  vs.  $430.5 \pm 3.5$  ng/dl,  $P < 0.01$ ) and SHBG ( $62.9 \pm 2.8$  vs.  $82.1 \pm 1.6$  ng/dl,



**FIG. 1.** Prevalence of the MS in BLSA men at entry. The number of subjects with MS and the total number of subjects in each age group are given in parentheses.

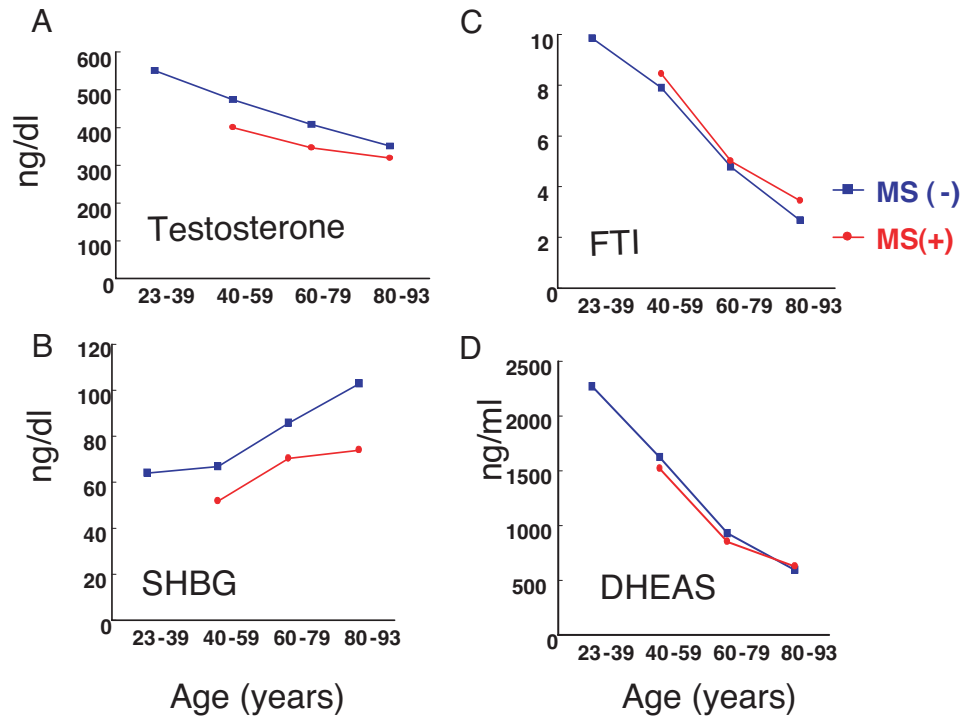


FIG. 2. Androgen levels in men stratified by age and the presence or absence of the MS at entry. Values for the mean values of the MS (+) group are not shown for the 23- to 39-yr age group because there were only four subjects in this category.

$P < 0.01$ ) levels were significantly lower in men with the MS, compared with men without the MS, respectively, whereas FTI levels were slightly higher in men with the MS ( $6.2 \pm 0.15$  vs.  $5.8 \pm 0.08$ ,  $P < 0.01$ ). Age-adjusted DHEAS levels were not significantly different between the two groups.

We next examined the longitudinal relationships between androgens and the development of the MS (defined with and without an abnormal 2hPG level) over a mean follow-up period of 5.8 yr. Table 2A shows the age, BMI, hormone, and SHBG measurements for the 417 men who were free of both MS and DM at baseline and who also had androgen levels measured. As shown in Table 2B, age *per se* did not significantly increase the risk of incident MS. However, BMI was

positively associated with a 24% increased risk for development of the MS ( $P < 0.0001$ ). Age- and BMI-adjusted total T and SHBG levels were negatively related to the risk for development of MS (~50% reduction,  $P < 0.0001$ ). The FTI was significantly positively related to the development of the MS ( $P < 0.0002$ ), whereas DHEAS levels had no effect. The effects of including an abnormal 2hPG (impaired glucose tolerance or DM) on the risk for incident MS (Table 3) were not significantly different from the risk using the current ATP III criteria for the MS (Table 2). The effect of baseline androgen levels on development of DM vs. the MS was significant only for SHBG levels adjusted for age and BMI (data not shown). For Tables 2B and 3B, the hazard ratio

TABLE 2. Development of the MS (ATP III) in subjects without the MS or DM at baseline for a mean follow-up period of 5.8 yr

		Range	
A. Cohort description			
	417		
Age (yr)	$59.6 \pm 0.8$	27–92	
BMI ( $\text{kg}/\text{m}^2$ )	$25.1 \pm 0.1$	19.0–37.7	
Total T (ng/dl)	$446.4 \pm 105.5$	86.7–812.2	
SHBG (ng/dl)	$67.8 \pm 31.8$	17.7–257.0	
FTI	$6.4 \pm 3.1$	–0.8–20.5	
DHEAS (ng/ml) (n = 413)	$1384.0 \pm 41.1$	137–4390	
B. Development of the MS (n = 99)			
	Hazards ratio	Confidence limits	P value
Age	1.00	0.98–1.01	0.63
BMI	1.24	1.18–1.31	0.0001
Total T	0.51 <sup>a</sup>	0.40–0.66	0.0001
	0.70 <sup>b</sup>	0.53–0.92	0.03
SHBG	0.45 <sup>a</sup>	0.33–0.62	0.0001
	0.58 <sup>b</sup>	0.44–0.78	0.0003
FTI	1.66 <sup>a</sup>	1.25–2.20	0.0004
	1.58 <sup>b</sup>	1.18–2.10	0.0002
DHEAS	1.00 <sup>a</sup>	1.00–1.00	0.56
	1.00 <sup>b</sup>	1.00–1.00	0.62

<sup>a</sup> Values adjusted for age.

<sup>b</sup> Values adjusted for age and BMI.

**TABLE 3.** Development of the MS (ATPIII plus abnormal 2hPG) in subjects without the MS or DM at baseline with MS hazard adjusted separately for four sets of covariates

		Range	
<b>A. Cohort description</b>			
	363		
Age	59.1 ± 0.8	27–92	
BMI	24.8 ± 0.2	19.0–37.7	
Total T (ng/dl)	454.0 ± 5.6	160.3–812.2	
SHBG (ng/dl)	67.9 ± 1.6	17.7–226.0	
FTI	6.4 ± 0.2	–0.8–20.5	
DHEAS (ng/ml) (n = 359)	1405.2 ± 45.1	137–4390	
<b>B. Development of the MS</b>			
	Hazards ratio	Confidence limits	P value
Age	1.01	0.99–1.02	0.27
BMI	1.24	1.17–1.31	0.0001
Total T	0.52 <sup>a</sup>	0.41–0.67	0.0001
	0.70 <sup>b</sup>	0.53–0.92	0.03
SHBG	0.49 <sup>a</sup>	0.37–0.65	0.0001
	0.58 <sup>b</sup>	0.44–0.78	0.0003
FTI	1.56 <sup>a</sup>	1.16–2.09	0.0004
	1.58 <sup>b</sup>	1.18–2.10	0.0002
DHEAS	1.00 <sup>a</sup>	1.00–1.00	0.57
	1.00 <sup>b</sup>	1.00–1.00	0.63

Univariate analysis.

<sup>a</sup> Values adjusted for age.

<sup>b</sup> Values adjusted for age and BMI.

represented the change in risk for the development of MS associated with an increase of 1 yr for age (*i.e.* 1 yr) and 1 U for BMI. For the androgens, the hazard ratio represents the change in risk for the development of MS associated with an increase of 1 sd.

We next examined the effects of the different covariates on the development of the MS using stepwise proportional hazards regression models. As shown in Table 4, BMI, SHBG, and total T were significant independent predictors for the development of the MS. The addition of each covariate in the stepwise proportional hazards regression model showed that the multivariate analyses were more predictive of the development of the MS, compared with the univariate analysis. However, there was not a significant difference among the covariates in the different models for the development of the MS.

## Discussion

Our previously published work suggested that men in the BLSA have a higher prevalence of the MS than women (2).

**TABLE 4.** Development of the MS (ATPIII) in subjects without the MS or DM at baseline: best three proportional hazards regression models by number of variables in the model (n = 417)

No. of variables	$\chi^2$	Variables included in model
1	72.02	BMI
1	19.45	SHBG
1	17.21	Total T
2	77.09	BMI, SHBG
2	75.11	BMI, total T
2	74.69	BMI, FTI
3	83.75	BMI, total T, FTI
3	80.62	BMI, total T, SHBG
3	80.38	Age, BMI, FTI
4	85.84	Age, BMI, total T, FTI
4	83.82	BMI, total T, SHBG, FTI
4	81.85	Age, BMI, SHBG, FTI
5	85.91	Age, BMI, total T, SHBG, FTI

In this current cohort of BLSA participants, the prevalence of the MS was significantly higher in middle-aged and older men as compared with that in younger men. Whereas there have been other published studies that have examined relationships between androgen levels and the MS (prevalence and incidence) (3, 4, 14–16), to date, none has reported increased prevalence of the MS across the broad age spectrum as shown in our cohort. Nonetheless, given the fact that many of the determinants of the MS (adiposity, glucose intolerance, and hypertension) are associated with aging, it is not too surprising that the MS is more prevalent in middle-aged and older men.

The cross-sectional association among aging, androgen levels, and the MS showed that total T and SHBG levels were significantly lower in men with the MS, compared with men without the MS. Specifically, total T levels decreased with aging, whereas SHBG levels increased with aging. In subjects with the MS, these trends were also apparent; however, the levels of total T and SHBG were lower, compared with men without the MS. However, DHEAS levels and FTI were not significantly different in men with and without the MS (Fig. 2, C and D). Our results are consistent with those reported by others (17, 18) in that the association of DHEAS on cardiovascular risk factors is inconsistent.

The limitation of the cross-sectional analysis is its inability to assign causality or detect cohort or secular trends. Does the MS decrease androgen levels or do lower androgen levels increase the prevalence of the MS? We attempted to answer this question by examining the relationships of androgen and SHBG levels to development (incidence) of the MS in men without the MS or DM at baseline as classified by ATPIII. We found the incidence of the MS to be associated with increased BMI but not with age, whereas age-adjusted total T and SHBG levels were negatively associated with incident MS. Further adjustment for BMI attenuated the protective effects of total T and SHBG, although levels remained significant.



The effect of an abnormal 2hPG level as a component of the MS did not alter the relations among age, BMI, or androgen levels on incident MS (Table 3).

Therefore, low baseline androgen levels appear to predict incident MS. Our results are consistent with those reported by Laaksonen *et al.* (4), in which these investigators also used the ATPIII criteria for classification of the MS. They found that men with total T, SHBG, or calculated free T in the lowest quartile had a significantly higher risk for development of the MS, compared with the remaining men (4). They also found that further adjustment for confounders, such as smoking, alcohol intake, socioeconomic status, cardiovascular disease, and exercise, did not diminish the association between baseline androgen levels and incident MS. However, BMI did attenuate the association, a finding we also observed. In the study by Laaksonen *et al.* (4), incident DM was also significantly increased in men with total T and SHBG in the lowest quartile. We did not see an association between total T levels and incident DM, but there was a significant association of SHBG with development of DM.

Kupelian *et al.* (16) also recently reported the relationship of androgens to the development of the MS in an age cohort of 40- to 70-yr-old men. Again, total T and SHBG were significantly related to the MS incidence, but FTI was unrelated. This prospective study is limited by the absence of fasting blood values for glucose and triglycerides at entry; thus, some subjects undoubtedly were already positive for MS at entry.

The limitations of our study warrant further discussion. Our population consists of middle- and upper-class Caucasians, who on average were close to the upper limit of desirable body weight (although, as expected, subjects with the MS were overweight and closer to being defined as obese). Androgen levels were obtained at a single visit, which likely affected risk assessments for incident MS and DM and risks for coronary heart disease and mortality. We detected a significant positive relationship between FTI and the MS, as has been reported in premenopausal women with polycystic ovarian syndrome (19) and younger postmenopausal women (20). In all these groups of women, increased (not decreased) free T is associated with increased total and abdominal fat, insulin resistance, and the MS. Whether increased free T in older men promotes augmented fat, insulin resistance, and the MS remains to be determined.

In conclusion, lower baseline androgen levels predict incident MS.

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