Endogenous Sex Hormones and Metabolic Syndrome in Aging Men

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Background: Sex hormone levels in men change during aging. These changes may be associated with insulin sensitivity and the metabolic syndrome.

Methods: We studied the association between endogenous sex hormones and characteristics of the metabolic syndrome in 400 independently living men between 40 and 80 yr of age in a cross-sectional study. Serum concentrations of lipids, glucose, insulin, total testosterone (TT), SHBG, estradiol (E_2), and dehydroepiandrosterone sulfate (DHEA-S) were measured. Bioavailable testosterone (BT) was calculated using TT and SHBG. Body height, weight, waist-hip circumference, blood pressure, and physical activity were assessed. Smoking and alcohol consumption was estimated from self-report. The metabolic syndrome was defined according to the National Cholesterol Education Program definition, and insulin sensitivity was calculated by use of the quantitative insulin sensitivity check index.

Results: Multiple logistic regression analyses showed an inverse relationship according to 1 SD increase for circulating TT [odds ratio (OR) = 0.43; 95% confidence interval (CI), 0.32–0.59], BT (OR = 0.62; 95% CI, 0.46–0.83), SHBG (OR = 0.46; 95% CI, 0.33–0.64), and DHEA-S (OR = 0.76; 95% CI, 0.56–1.02) with the metabolic syndrome. Each SD increase in E_2 levels was not significantly associated with the metabolic syndrome (OR = 1.16; 95% CI, 0.92–1.45). Linear regression analyses showed that higher TT, BT, and SHBG levels were related to higher insulin sensitivity; β-coefficients (95% CI) were 0.011 (0.008–0.015), 0.005 (0.001–0.009), and 0.013 (0.010–0.017), respectively, whereas no effects were found for DHEA-S and E_2. Estimates were adjusted for age, smoking, alcohol consumption, and physical activity score. Further adjustment for insulin levels and body composition measurements attenuated the estimates, and the associations were similar in the group free of cardiovascular disease and diabetes.

Conclusions: Higher testosterone and SHBG levels in aging males are independently associated with a higher insulin sensitivity and a reduced risk of the metabolic syndrome, independent of insulin levels and body composition measurements, suggesting that these hormones may protect against the development of metabolic syndrome. (*J Clin Endocrinol Metab* **90:** 2618–2623, 2005)

T HE METABOLIC SYNDROME represents a constellation of lipid and nonlipid risk factors of metabolic origin and is closely linked to a generalized metabolic disorder called insulin resistance in which the normal actions of insulin are impaired (1, 2). The syndrome is most important because of its association with subsequent development of type 2 diabetes mellitus and cardiovascular disease (CVD) (2, 3). The pathogenesis of the syndrome is multifactorial, but obesity and sedentary lifestyle and factors in concert with diet and still largely unknown genetic factors interact in the occurrence of the syndrome (3).

Decline of both testicular and adrenal function with aging causes a decrease in androgen concentrations in men (4). Epidemiological evidence has shown that sex steroid hormones are related to type 2 diabetes and CVD in men in some but not all studies (5–9). Although the mechanisms underlying the association between endogenous sex hormone levels and both diabetes and CVD are not entirely understood, it has been postulated that low levels of total testosterone (TT), bioavailable testosterone (BT), SHBG, and dehydroepiandrosterone sulfate (DHEA-S) are associated with unfavorable levels of several strong CVD risk factors, such as lipids (10–13) and blood pressure (8, 11, 14), which are components of the metabolic syndrome, and insulin levels (15–17). To our knowledge, no data exist linking endogenous sex hormone levels to the metabolic syndrome.

The aim of this large-scale cross-sectional study was to investigate the relation of endogenous testosterone, SHBG, DHEA-S, and estradiol (E_2) with metabolic syndrome, as defined by the National Cholesterol Education Program (NCEP), in middle-aged and elderly men.

Subjects and Methods

Subjects

The study is a cross-sectional, single-center study in 400 independently living men aged 40–80 yr. The subjects were recruited by means of asking female participants of other studies conducted by the Julius center by letter whether they knew a possible interested male volunteer between the age of 40 and 80. Invitation letters were sent to 770 female participants. Because of this indirect way of recruiting, it was not possible to assess the exact participation rate for this group. However, 240 men volunteered for participation.

Next, names and addresses of a randomly selected male population

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aged 40–80 yr were drawn from the municipal register of Utrecht, a large-sized town in the middle part of The Netherlands, and 1230 invitation letters were sent to male inhabitants of Utrecht by means of a selection from the municipal register. From this group, 390 men volunteered for participation (participation rate of 31.7%). From the 630 volunteers, we excluded those who did not live independently and subjects who were not physically or mentally able to visit the study center independently (n = 16). No additional health-related eligibility criteria were used. Of the remaining 614 men, eventually 400 men were randomly selected to participate. To yield equal numbers in each age-decade from the age of 40–80, we sampled 100 men in each decade of age. All participants gave written informed consent before enrollment in the study, and the institutional review board of the University Medical Center Utrecht approved the study.

Procedure

Data collection took place between March 2001 and April 2002. During two visits to the study center, medical histories were obtained, including a self-reported physician diagnosis, a venipuncture was performed between 0800 and 1000 h, and fasting blood samples were obtained. Platelet-free serum was obtained by centrifugation and immediately stored at −20 C.

Hormone determinations

Levels of steroid were measured in serum. TT was measured after diethylether extraction using an in-house competitive RIA employing a polyclonal antitestosterone antibody (AZG 3290; Dr. J. H. Pratt, Indianapolis, IN). [$1\alpha,2\alpha$-^{3}H]Testosterone (DuPont NEN, Boston, MA) was used as a tracer after chromatographic verification of its purity. The lower limit of detection was 0.24 nmol/liter, and interassay variation was 6.0, 5.4, and 8.6% at 2.1, 5.6, and 23 nmol/liter, respectively (n = 85). SHBG was measured using an immunometric technique on an IMMULITE analyzer (Diagnostic Products Corp., Los Angeles, CA). The lower limit of detection was 5 nmol/liter, and interassay variation was 6.1, 4.9, and 6.9% at 11.6, 36, and 93 nmol/liter, respectively (n = 30). BT was calculated from SHBG and TT using the method of Vermeulen *et al.* (18). Total E$_2$ was measured after diethylether extraction and Sephadex chromatography using an in-house competitive RIA employing a polyclonal anti-E$_2$ antibody (Dr. F. de Jong, Erasmus Medical Center, Rotterdam, The Netherlands). [$2,4,6,7$-^{3}H]E$_2$ (Amersham Biosciences Europe GmbH, Roosendaal, The Netherlands B.V.) was used as a tracer after chromatographic verification of its purity. The lower limit of detection was 20 pmol/liter (2-ml sample), and interassay variation was 10.0 and 3.1% at 81 and 660 pmol/liter, respectively (n = 24 and 17, respectively). DHEA-S was measured using an immunometric technique on an Advantage Chemiluminescense System (Nichols Institute Diagnostics, San Juan Capistrano, CA). The lower limit of detection was 0.1 μmol/liter, and interassay variation was 5.2, 5.6, and 4.2% at 1.0, 4.9, and 14.2 μmol/liter, respectively (n = 19).

Risk factors

During the examination, height and weight were measured in standing position without shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the level midway between the lower rib margin and the iliac crest with participants in standing position, breathing out gently. Peripheral blood pressure was measured twice in the right brachial artery with a semiautomated device (Dinamap, GE HealthCare, Tampa, FL). The average of the two measurements of systolic and diastolic blood pressure was used for analysis and further calculation. An automatic enzymatic procedure was used to determine serum total cholesterol (Synchron LX Systems; Beckman Coulter, Mijdrecht, The Netherlands). High-density lipoprotein (HDL) cholesterol and triglycerides were measured similarly. Fasting glucose levels were assessed using a GlucoTouch reflectometer (LifeScan, Inc., Benelux, Beese, Belgium), a reagent-strip glucose oxidase method. Venous whole blood was immediately applied to the test strip. Fasting insulin levels (mIU/liter) were measured using an IMMULITE 2000 analyzer (Diagnostic Products Corp., Los Angeles, CA). The lower limit of detection was 2 mIU/liter, and interassay variation was 8.6, 4.8, 4.4, 5.1, and 5.4% at 14, 27, 86, 175, and 354 mIU/liter, respectively.

Metabolic syndrome

The metabolic syndrome according to the NCEP (1) was defined as present when three or more of the following criteria were met: fasting plasma glucose of at least 6.1 mmol/liter (110 mg/dl), serum triglycerides of at least 1.7 mmol/liter (150 mg/dl), serum HDL cholesterol less than 1.0 mmol/liter (40 mg/dl), blood pressure of at least 130/85 mm Hg or antihypertensive medication use, or waist girth of more than 102 cm. This applied to 24% of the participants.

Insulin sensitivity

To assess insulin sensitivity, we calculated the quantitative insulin sensitivity check index (QUICKI), which has a high correlation with insulin sensitivity measured with the glucose clamp technique (19). QUICKI can be determined from fasting insulin and glucose values according to the equation: QUICKI = $1/[\log (I0) + \log (G0)]$, in which I0 is fasting insulin (mIU/liter) and G0 is fasting glucose (mg/dl = mmol/liter × 18.182).

Other variables

Participants were asked about current use of medications, and these reports were checked by examining labels of drugs brought to the clinic. Diabetes mellitus was defined as treatment with insulin or oral hypoglycemic agents. Prevalent CVD was defined as a pooled condition including coronary heart disease, peripheral artery disease, and stroke, which was defined as present when men reported a history of these conditions with diagnosis and treatment. Smoking was estimated from self-report and was categorized as current, former, or never. The subject's customary alcohol intake was estimated from a validated food frequency questionnaire (20) and was categorized as 0, 0–20, 20–40, or more than 40 g/d alcohol consumption. Physical activity was assessed using a questionnaire that was validated in an elderly population (21).

Data analysis

Logistic regression was used to estimate the odds ratios (OR) and 95% confidence interval (CI) for the presence of the separate risk factors of metabolic syndrome included in the NCEP definition. The independent variables of interest were TT, BT, SHBG, DHEA-S, and E$_2$. We adjusted logistic regression models for age, smoking (current, else), alcohol consumption (grams/day), physical activity, and for all other risk factors included in the NCEP definition of metabolic syndrome.

Multivariate models using analysis of covariance were used to estimate mean sex hormone levels with 95% CI across categories of risk factors (0, 1, 2, and ≥3) according to the NCEP definition of metabolic syndrome. Trend analyses were done using linear regression models. Estimates were adjusted for age, smoking, alcohol consumption, and physical activity. To rule out the influence of systemic illness on sex hormone levels we repeated analyses of covariance in a subgroup of subjects without prevalent diabetes mellitus (n = 21) and CVD (n = 68).

Logistic regression was used to quantify the effect of sex hormone levels on the presence of the metabolic syndrome by use of OR and its 95% CI. The independent variables of interest were TT, BT, SHBG, DHEA-S, and E$_2$. We adjusted regression models for age, smoking, alcohol consumption, and physical activity (model 1). To evaluate the association of sex hormones and metabolic syndrome independently of insulin levels and body composition measurements, we additionally adjusted logistic regression models for insulin (model 2) and waist circumference and BMI (model 3).

Linear regression analysis was used to estimate the relation of circulating sex hormone levels with insulin levels and insulin sensitivity (assessed with QUICKI). We adjusted regression models for age, smoking, alcohol consumption, and physical activity. To elucidate whether and to what extent the observed associations of sex hormone levels with insulin sensitivity might be explained by intermediates, further analysis also adjusted for body composition measurements (waist girth and BMI). Statistical analyses were performed using SPSS for Windows (version 11.5).

Results

The characteristics of the study population are presented in Table 1. The median age of the total study group was 60

TABLE 1. Characteristics of the study sample (N = 400)

Characteristic	Mean ± SD
Age (yr)	60.2 ± 11.3
BMI (kg/m^2)	26.3 ± 3.5
Waist (cm)	98.9 ± 9.4
Smoking, current (%)	20
Alcohol consumption (g/d)	20.2 ± 21.5
Physical activity (Voorrips score)	18.7 ± 7.5
Systolic blood pressure (mm Hg)	143.4 ± 22.1
Diastolic blood pressure (mm Hg)	81.6 ± 11.0
Cholesterol, total (mmol/liter)	5.8 ± 1.1
Cholesterol, HDL (mmol/liter)	1.3 ± 0.3
Triglycerides (mmol/liter)	1.5 ± 1.0
Glucose (mmol/liter)	6.0 ± 1.5
Insulin (mIU/liter)	8.4 ± 5.9
Insulin sensitivity (QUICKI)	0.35 ± 0.04
Diabetes (%)	5.3
CVD (%)	17
Sex hormones	
TT (nmol/liter)	18.5 ± 5.3
BT (nmol/liter)	8.1 ± 2.2
SHBG (nmol/liter)	40.6 ± 14.5
DHEA-S (μmol/liter)	6.7 ± 3.3
E$_2$ (pmol/liter)	91.3 ± 22.8

Data represent mean ± SD or percentages. For some men, data were missing on total and HDL cholesterol and glucose (n = 1), triglycerides (n = 4), and alcohol consumption and physical activity (n = 4).

yr (range, 40–80 yr). Twenty percent of the participants were current smokers, 58% were former smokers, and 22% had never smoked. Mean sex hormone levels were in line with results from other studies (6, 10, 13). The diagnosis of the metabolic syndrome is made when three or more of the risk determinants shown in Table 2 are present. In this population, 19% had no risk factors, 31% had one risk factor, 26% had two risk factors, and 24% had three or more risk factors.

Risk factors

An inverse relationship was observed for TT, BT, and SHBG, with risk factors of the metabolic syndrome (Table 3). Each SD (5.3 nmol/liter) increase in TT was associated with a 38% reduced risk of having a high waist girth (OR = 0.62; 95% CI, 0.47–0.83), a 37% reduced risk of having a low HDL levels (OR = 0.63; 95% CI, 0.42–0.92), a 37% reduced risk of having high fasting glucose levels (OR = 0.63; 95% CI, 0.47–0.84), and a 17% reduced risk of having high blood pressure (OR = 0.83; 95% CI, 0.65–1.07). Each SD (14.5 nmol/liter) increase in SHBG was associated with a 20–30% reduced risk of having high waist girth, high triglyceride levels, low HDL levels, high fasting glucose levels, or high blood pressure

TABLE 2. Identification of the metabolic syndrome in this study (N = 400)

Risk factor	Defining level[a]	Prevalence in this study
Abdominal obesity (waist circumference)	>102 cm	30%
Triglycerides	≥1.7 mmol/liter	26%
HDL cholesterol	<1.0 mmol/liter	14%
Fasting glucose	≥6.1 mmol/liter	28%
Blood pressure	≥130/85 mm Hg or medication	67%
≥3 risk factors		24%

[a] NCEP definition.

(Table 3). An increase in DHEA-S levels was statistically significantly associated only with a reduced risk of having a high waist girth (OR = 0.68; 95% CI, 0.51–0.92). Each SD (22.8 pmol/liter) increase in E$_2$ levels was associated with a 45% increased risk of having a high waist girth (OR = 1.45; 95% CI, 1.15–1.83), a 26% increased risk of having high triglyceride levels (OR = 1.26; 95% CI, 0.98–1.61), and a 36% reduced risk of low HDL levels (OR = 0.64; 95% CI, 0.45–1.91) (Table 3).

Figure 1 shows the adjusted mean (95% CI) for TT, SHBG, DHEA-S, and E$_2$. Adjusted mean (95% CI) BT levels for 0, 1, 2, and 3 or more risk factors were 8.5 (8.1–9.0), 8.3 (7.9–8.6), 8.2 (7.8–8.6), and 7.6 (7.2–8.0) nmol/liter, respectively (P for trend < 0.001). The number of risk factors increased with lower circulating T, SHBG, and DHEA-S levels (P value for linear trend was <0.001, 0.01, 0.001, and 0.04, respectively), and with higher E$_2$ levels (P value for linear trend was 0.04). Exclusion of subjects with prevalent diabetes and CVD did not change the observed estimates (data not shown).

Insulin sensitivity

Linear regression analyses showed that higher TT, BT, DHEA-S, and SHBG levels were associated with lower fasting insulin levels. Higher TT, BT, and SHBG levels were associated with higher insulin sensitivity (Table 4), whereas no effects were found for DHEA-S and E$_2$. After further adjustment for waist girth and BMI, higher levels of E$_2$ were associated with higher insulin sensitivity (β = 0.003; 95% CI, 0.00–0.006). The relations of TT, BT and SHBG with insulin levels were attenuated; linear regression coefficients (95% CI) were −0.72 (−1.28 to −0.15), −0.24 (−0.85 to 0.36), and −0.98 (−1.54 to −0.40), respectively. Similar effects were seen for the association between TT, BT, and SHBG with insulin sensitivity; linear regression coefficients (95% CI) were 0.006 (0.002–0.009), 0.000 (−0.003–0.004), and 0.009 (0.005–0.012), respectively.

Metabolic syndrome

Multiple logistic regression analyses showed an inverse relationship for TT, BT, SHBG, and DHEA-S with metabolic syndrome (Table 5). Each SD (5.3 nmol/liter) increase in TT was associated with a 57% reduced risk of having the metabolic syndrome (OR = 0.43; 95% CI, 0.32–0.59). Each SD (14.5 nmol/liter) increase in SHBG was associated with a 54% reduced risk of having the metabolic syndrome (OR = 0.46; 95% CI, 0.33–0.64) (Table 4). When both TT and SHBG were entered in the multivariate model, the independent reduced risk of having the metabolic syndrome was 46% for TT according to 1 SD increase (OR = 0.54; 95% CI, 0.37–0.79) and 31% for SHBG according to 1 SD increase (OR = 0.69; 95% CI, 0.46–1.03).

E$_2$ levels were not significantly associated with the risk of having the metabolic syndrome (OR = 1.16; 95% CI, 0.92–1.45). Adjustment for insulin levels (model 2) and body composition measurements (BMI and waist circumference; model 3) did attenuate the estimates, suggesting that the relation for TT, BT, SHBG, DHEA-S, and E$_2$ with metabolic syndrome was partly explained by insulin levels (Table 5). When adjustments were made for both insulin levels and

TABLE 3. Adjusted OR (95% CI) for the risk of the separate risk factors to a 1 SD increase in sex hormones

	SD	Waist >102 cm	Triglyceride ≥1.7 mmol/liter	HDL <1.0 mmol/liter	Glucose ≥6.1 mmol/liter	Blood pressure ≥130/85 mm Hg or medication
TT (nmol/liter)	5.3	0.62 (0.47–0.83)	0.86 (0.64–1.16)	0.63 (0.43–0.92)	0.63 (0.47–0.84)	0.83 (0.65–1.07)
BT (nmol/liter)	2.2	0.73 (0.55–0.97)	1.05 (0.79–1.41)	0.71 (0.48–1.05)	0.74 (0.55–0.99)	0.95 (0.73–1.23)
SHBG (nmol/liter)	14.5	0.71 (0.54–0.95)	0.72 (0.53–0.98)	0.71 (0.48–1.04)	0.70 (0.53–0.94)	0.78 (0.60–1.02)
DHEA-S (μmol/liter)	3.3	0.68 (0.51–0.92)	0.85 (0.62–1.15)	0.89 (0.57–1.38)	1.13 (0.85–1.51)	1.00 (0.76–1.31)
E_2 (pmol/liter)	22.8	1.45 (1.15–1.83)	1.26 (0.98–1.61)	0.64 (0.45–0.91)	0.97 (0.76–1.23)	1.09 (0.85–1.38)

ORs were adjusted for age, smoking, alcohol consumption, physical activity, and for the other risk factors of the metabolic syndrome.

body composition, only an increase in TT and SHBG were associated with a reduced risk of having the metabolic syndrome; the OR were, respectively, 0.64 (95% CI, 0.45–0.91) and 0.65 (95% CI, 0.45–0.93), suggesting that only TT and SHBG are independently associated with the metabolic syndrome.

Discussion

This population-based cross-sectional study of middle-aged and elderly men showed that serum levels of low endogenous TT, BT, SHBG, and DHEA-S were related to the metabolic syndrome, lower insulin sensitivity, and higher fasting serum insulin levels. TT and SHBG levels were associated with all separate components of the metabolic syndrome, whereas E_2 levels were associated only with body fat distribution and triglyceride levels. Furthermore, we observed that DHEA-S levels were significantly associated only with waist circumference. However, the number of risk factors increased significantly with lower circulating DHEA-S levels. Adjustment for fasting insulin levels and body composition measurements attenuated the associations between

sex hormones and metabolic syndrome, suggesting that apart from a direct effect of endogenous sex hormone levels on the metabolic syndrome and its risk factors, lower sex hormone levels might be particularly associated with insulin levels, insulin sensitivity, and obesity, which in turn are strongly related to the metabolic syndrome. The associations could not be explained by age, smoking, alcohol consumption, and physical activity.

To appreciate these findings, some issues need to be addressed. Strengths of the present study include that, to our knowledge, this study is the first study to date to assess the association between circulating sex hormone levels and the presence of the metabolic syndrome in independently living men across a wide age range. In this study, blood samples were obtained between 0800 and 1000 h, which is necessary to obtain reliable measurements because of the possible daily variation of sex hormones (22).

The interpretability of the results may be restricted by several factors inherent to the cross-sectional design, which limits conclusions regarding within-person change or direction of causality. Another concern is that because of within-
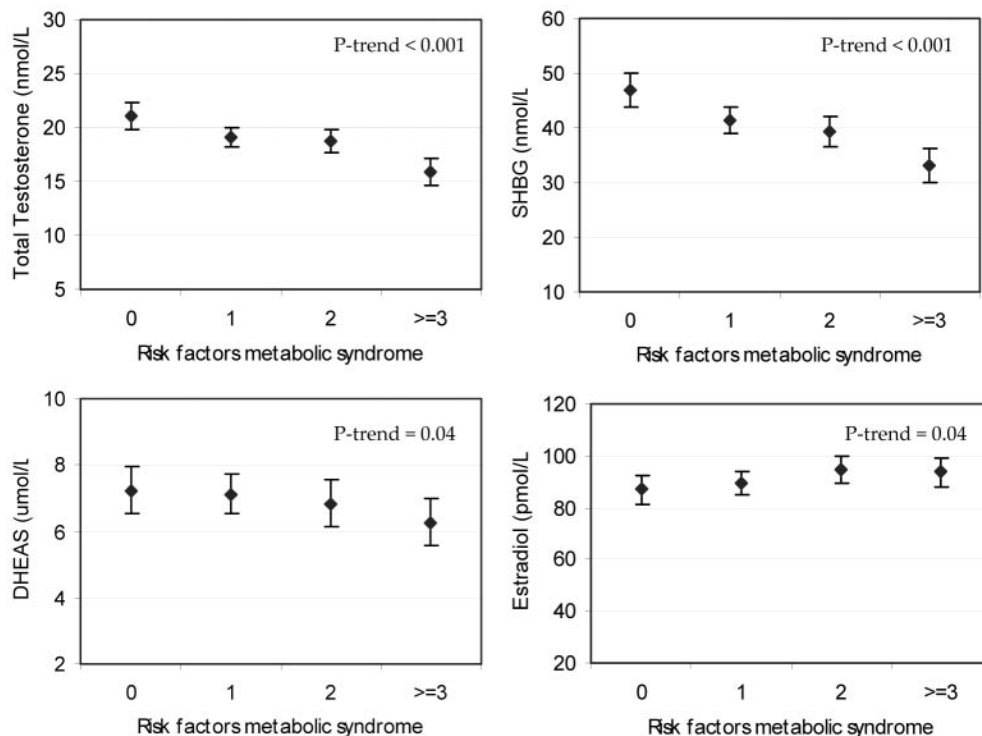

FIG. 1. Adjusted mean (95% CI) endogenous sex hormone levels for categories of number of risk factors according to the NCEP definition for metabolic syndrome and the *P* value for trend. Mean sex hormone levels were adjusted for age, smoking (pack-years), alcohol consumption (grams/day), and physical activity score.

TABLE 4. Adjusted linear regression coefficients (95% CI) for the relation of sex hormones (1 SD increase) with insulin levels and insulin sensitivity (QUICKI)

	SD	Insulin levels		Insulin sensitivity	
		β	95% CI	β	95% CI
TT (nmol/liter)	5.3	−1.53	−2.13 to −0.94	0.011	0.008–0.015
BT (nmol/liter)	2.2	−0.84	−1.51 to −0.18	0.005	0.001–0.009
SHBG (nmol/liter)	14.5	−1.63	−2.25 to −1.02	0.013	0.010–0.017
DHEA-S (μmol/liter)	3.3	−0.71	−1.40 to −0.03	0.002	−0.002–0.006
E_2 (pmol/liter)	22.8	0.26	−0.31 to 0.83	0.000	−0.004–0.003

Linear regression coefficients were adjusted for age, smoking, alcohol consumption, and physical activity.

subject biological variation, the single measurement of both sex hormones and several risk factors will reflect long-term averages less precisely than repeated measurements. However, this misclassification is likely to be random and will in most cases lead to an underestimation of the associations.

The association between low endogenous sex hormone levels and increased risk of metabolic syndrome is in line with several observational studies on endogenous sex hormones and cardiovascular risk factors (8, 10, 11, 13, 14, 16, 17, 23). Cross-sectional studies have found high T and SHBG levels to be associated with high HDL-cholesterol levels (10, 11). A longitudinal analysis of multiple risk factor intervention trial confirmed this relationship (13). Furthermore, this study showed that a decrease in endogenous T is associated with an increase in triglycerides. Concerning the association between sex hormones and blood pressure, research findings suggest a relationship between essential hypertension and impaired T levels in men (8, 14, 23). We observed that E_2 levels were not significantly associated with metabolic syndrome and its risk factors. However, other studies have suggested that the levels of E_2 within the physiological range of healthy men may help maintain a desirable profile of lipid and glucose metabolism (24).

Numerous studies support the biological plausibility of the relationship between sex hormones and metabolic syndrome (13, 25, 26). It is hypothesized that testosterone is directly related to HDL-cholesterol by increasing the hepatic production of apolipoprotein A-I, the major protein constituent of nascent high-density lipoprotein particles (13). The effect of endogenous testosterone on triglyceride levels may in turn be secondary to testosterone effects on body fat distribution, insulin and glucose metabolism. Several lines of evidence support an association between hypogonadism and insulin sensitivity in men. Low circulating levels of testosterone are observed in obesity, which is accompanied by insulin resistance (27).

Furthermore, administration of testosterone to hypogonadal rats (26) or humans (28) has resulted in reductions of both abdominal obesity and insulin resistance, as measured by the glucose clamp technique, and glucose and lipid profiles improved (29–31). In contrast, testosterone supplementation can lead to depressed SHBG levels, which in time can lead to an unfavorable cardiovascular risk profile and metabolic syndrome (10). This indicates that caution has to be taken with (supraphysiological) testosterone supplementation (32). On the other hand, it has been suggested that insulin is capable of stimulating testosterone production and, simultaneously, of inhibiting SHBG concentrations in men. It is not known whether the observed relationship between low plasma testosterone is direct or indirect, because the relationship between testosterone and insulin is not fully understood (15). Furthermore, low circulating testosterone levels might, through compensatory hyperinsulinemia, generate hypertension (25).

An important question is whether the relationship between metabolic syndrome and hormones is only a reflection of confounding with body weight. A likely finding is that central obesity and insulin resistance and the effects on SHBG are driving the association of hormone levels and metabolic syndrome. However, after adjusting for insulin levels and body composition measurements, increases in endogenous TT and SHBG levels are still independently associated with reduced risk of metabolic syndrome.

Systemic disease has been shown to influence male gonadal function (33), and it could be hypothesized that because of the presence of CVD or diabetes, sex hormone levels decrease. An important question, therefore, is whether lower levels of sex hormones that were related to a higher prevalence of metabolic syndrome are cause or effect. In an attempt to answer this question, we subdivided the cohort by presence or absence of prevalent diabetes and CVD. Adjusted mean sex hormone levels for categories of risk factors did not

TABLE 5. Adjusted OR (95% CI) for the risk of metabolic syndrome to a 1 SD increase in sex hormones

	SD	Risk of metabolic syndrome			
		Crude	Model 1[a]	Model 2[b]	Model 3[c]
TT (nmol/liter)	5.3	0.40 (0.29–0.54)	0.43 (0.32–0.59)	0.56 (0.40–0.79)	0.58 (0.41–0.81)
BT (nmol/liter)	2.2	0.60 (0.46–0.78)	0.62 (0.46–0.83)	0.73 (0.52–1.01)	0.77 (0.55–1.07)
SHBG (nmol/liter)	14.5	0.54 (0.41–0.71)	0.46 (0.33–0.64)	0.59 (0.42–0.85)	0.57 (0.40–0.81)
DHEA-S (μmol/liter)	3.3	0.77 (0.60–0.98)	0.76 (0.56–1.02)	0.81 (0.58–1.13)	0.92 (0.66–1.29)
E_2 (pmol/liter)	22.8	1.16 (0.93–1.45)	1.16 (0.92–1.45)	1.17 (0.91–1.52)	0.97 (0.75–1.24)

Metabolic syndrome was defined according to the NCEP definition.

[a] Model 1: OR was adjusted for age, smoking, alcohol consumption, and physical activity.

[b] Model 2: OR was adjusted for age, smoking, alcohol consumption, physical activity, and insulin levels (mU/liter).

[c] Model 3: OR was adjusted for age, smoking, alcohol consumption, physical activity, BMI, and waist circumference.

change (data not shown), suggesting that the findings were not a result of prevalent diabetes and CVD and would be compatible but with the view that low sex hormone levels are indeed causally related to disease. Follow-up studies and preferably intervention studies should be performed to clarify the complex relationships among TT, BT, SHBG, DHEA-S, E_2, insulin, and cardiovascular risk factors in men.

In summary, low endogenous TT and SHBG levels appear to increase the risk of metabolic syndrome in middle-aged and elderly men independently of fasting insulin levels and body composition measurements, and low levels of these sex hormones are related to lower insulin sensitivity and higher fasting insulin levels, suggesting that these hormones might play a protective role in the development of metabolic syndrome and insulin resistance and subsequent diabetes mellitus and CVD in aging men. However, a causal interpretation of our findings is inherently restricted by the cross-sectional nature of the design.

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