Association of Testosterone and Sex Hormone–Binding Globulin With Metabolic Syndrome and Insulin Resistance in Men

CHAOYANG LI, MD, PHD[1]
EARL S. FORD, MD, MPH[1]
BENYI LI, MD, PHD[2]
WAYNE H. GILES, MD, MS[1]
SIMIN LIU, MD, SCD[3]

OBJECTIVE — We sought to assess the associations of testosterones and sex hormone–binding globulin (SHBG) with metabolic syndrome and insulin resistance in men.

RESEARCH DESIGN AND METHODS — We defined metabolic syndrome according to the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Among men aged ≥20 years who participated in the Third National Health and Nutrition Examination Survey (n = 1,226), the Cox proportional hazards model was used to estimate the prevalence ratio and 95% CI of metabolic syndrome according to circulating concentrations of testosterones and SHBG.

RESULTS — After adjustment for age, race/ethnicity, smoking status, alcohol intake, physical activity level, LDL cholesterol, C-reactive protein, and insulin resistance, men in the first quartile (lowest) (prevalence ratio 2.16 [95% CI 1.53–3.06]) and second quartile of total testosterone (2.51 [1.86–3.37]) were more likely to have metabolic syndrome than men in the fourth quartile (highest, referent group) ($P < 0.001$ for linear trend). Similarly, men in the first quartile of SHBG (2.17 [1.32–3.56]) were more likely to have metabolic syndrome than men in the fourth quartile ($P = 0.02$ for linear trend). No significant associations of calculated free testosterone ($P = 0.31$ for linear trend) and bioavailable testosterone ($P = 0.11$ for linear trend) with metabolic syndrome were detected after adjustment for all possible confounders.

CONCLUSIONS — Low concentrations of total testosterone and SHBG were strongly associated with increased likelihood of having metabolic syndrome, independent of traditional cardiovascular risk factors and insulin resistance.

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Testosterone, synthesized and produced by the Leydig cells of the testes, is the predominant sex hormone in men. Sex hormone–binding globulin (SHBG), produced by the liver, is a circulating steroid-transporting protein. In the general circulation, total testosterone is currently classified into four major fractions: SHBG-bound testosterone (~44%), albumin-bound testosterone (~50%), cortisol-binding globulin–bound testosterone (~4%), and unbound or free testosterone (~2%) (1). Free and albumin-bound testosterones are thought to be readily available to the tissues of the body (i.e., bioavailable testosterone). Aging men are characterized by a decrease in circulating testosterone concentrations (2), and testosterone deficiency (or late-onset hypogonadism or andropause), and low SHBG levels have been associated with increased risk of type 2 diabetes (3).

Insulin resistance is known to be closely related to both metabolic syndrome (4) and sex hormone concentrations (5). Recently, several cross-sectional studies (6–8) have also linked low levels of testosterone and SHBG to metabolic syndrome or its specific components. A few prospective studies have investigated the direct relationships between testosterone and SHBG as predictors for the risk of metabolic syndrome (9–11). However, previous studies have been limited by the lack of comprehensive assessment of insulin resistance and free testosterone levels and the lack of generalizability due to their focus on special populations such as patients with sexual dysfunction or participants in restricted geographic areas. To further assess the role of testosterone and SHBG in relation to metabolic syndrome and insulin resistance in the general population, we analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III), in which all these measures were available in this nationally representative sample of men in the U.S.

RESEARCH DESIGN AND METHODS

— A representative sample of the civilian noninstitutionalized U.S. population was recruited into NHANES III (1988–1994) with a multistage, stratified sampling design (12). NHANES III oversampled non-Hispanic blacks, Mexican Americans, and adults aged ≥60 years to ensure enough data and reliable estimates in these subpopulations. Response rates were 86% for the household interviews and 78% for the medical examinations. Blood was drawn after an overnight fast for participants in the morning sample. After centrifugation, serum samples were aliquotted and stored at −70°C until they were quantified. The serum samples were shipped on dry ice directly to the assay laboratory. In the present study, NHANES III Survey Phase I (1988–1991) data (n = 1,470 men aged ≥20 years) were analyzed. After exclusion of participants who had fasted <8 h (n = 101) and had missing data on all covariates (n = 143), the analytic sample (n = 1,226, 83.4%) com-

From the [1]Division of Adult and Community Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; the [2]Department of Urology, University of Kansas Medical Center, Kansas City, Kansas; and the [3]Departments of Epidemiology and Medicine, Center for Metabolic Disease Prevention, University of California, Los Angeles, Los Angeles, California.
Corresponding author: Chaoyang Li, cli@cdc.gov.
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prises 573 non-Hispanic whites (77.9%), 297 non-Hispanic blacks (9.5%), 307 Mexican Americans (5.1%), and 49 participants with all other race/ethnicity (7.5%).

Table 1—*Geometric means of fasting serum insulin and HOMA-IR by the quartiles of total testosterone, SHBG, CFT, and CBT in U.S. men ≥20 years of age, NHANES III Phase I, 1988–1991*

	n	Geometric mean (95% CI)*	
		Fasting serum insulin	HOMA-IR
Total testosterone (nmol/l)			
1st quartile (0.2–14.2)	351	10.59 (9.49–11.83)	2.73 (2.42–3.08)
2nd quartile (14.2–18.2)	308	10.61 (9.88–11.40)	2.62 (2.43–2.83)
3rd quartile (18.2–22.9)	289	7.18 (6.54–7.88)	1.74 (1.58–1.92)
4th quartile (22.9–47.0)	278	6.98 (6.43–7.58)	1.68 (1.54–1.83)
P value		<0.001	<0.001
SHBG (nmol/l)*			
1st quartile (9.7–25.2)	259	10.70 (9.54–11.99)	2.71 (2.38–3.08)
2nd quartile (25.2–34.6)	292	9.60 (8.82–10.45)	2.41 (2.20–2.65)
3rd quartile (34.6–47.1)	299	7.90 (7.41–8.42)	1.93 (1.80–2.06)
4th quartile (47.1–198.3)	376	6.90 (6.32–7.55)	1.65 (1.51–1.81)
P value†		<0.001	<0.001
CFT (nmol/l)‡			
1st quartile (0.0–0.3)	397	9.74 (8.56–11.10)	2.40 (2.07–2.78)
2nd quartile (0.3–0.4)	279	9.29 (8.63–9.99)	2.32 (2.14–2.51)
3rd quartile (0.4–0.5)	255	8.38 (7.63–9.20)	2.06 (1.86–2.28)
4th quartile (0.5–1.1)	295	7.59 (6.64–8.67)	1.87 (1.61–2.16)
P value		0.02	0.02
CBT (nmol/l)‡			
1st quartile (0.0– 6.4)	412	9.85 (8.52–11.38)	2.42 (2.05–2.86)
2nd quartile (6.5– 8.7)	294	9.23 (8.61–9.88)	2.32 (2.15–2.50)
3rd quartile (8.7–11.0)	247	8.28 (7.48–9.17)	2.04 (1.83–2.26)
4th quartile (11.0–24.0)	273	7.51 (6.46–8.72)	1.83 (1.55–2.17)
P value		0.02	0.03

Data are geometric means (95% CI) of fasting serum insulin and HOMA-IR, adjusted for age, race, smoking status, alcohol intake, physical activity level, LDL cholesterol, and CRP. *To convert nanomoles per liter to nanograms per milliliter, divide by 3.4. †*P* values were estimated in the *t* test of deviation from linear trend for fasting serum insulin and HOMA-IR. ‡Estimated according to the methods proposed by Vermeulen et al. (14).

Measurements

Sex steroid hormone concentrations. Serum concentrations of total testosterone and SHBG were measured using competitive electrochemiluminescence immunoassays on the Elecsys 2010 autoanalyzer (Roche Diagnostics, Indianapolis, IN). The lowest detection limits of the assays were 0.02 ng/ml for total testosterone and 3 nmol/l for SHBG. The coefficients of variation were 5.9 and 5.8% at 2.5 and 5.5 ng/ml for total testosterone and 5.3 and 5.9% at 5.3 and 16.6 nmol/l for SHBG. Detailed laboratory methods, quality-control procedures, and mean concentrations of testosterone and SHBG have been reported previously (13). Calculated free testosterone (CFT) and calculated bioavailable testosterone (CBT) concentrations were obtained from serum total testosterone, SHBG, and albumin concentrations using the methods proposed by Vermeulen et al. (14).

Measures of metabolic syndrome components and other biochemical markers. Waist circumference of participants was measured at the high point of the iliac crest at minimal respiration to the nearest 0.1 cm. Averages of the second and the third systolic blood pressure and diastolic blood pressure readings were used in the analyses. Serum total cholesterol was measured enzymatically in a series of coupled reactions that hydrolyze cholesterol esters and oxidize the 3-hydroxy group of cholesterol. Serum triglycerides were measured enzymatically after hydrolysis to produce glycerol. The HDL cholesterol concentration was measured after precipitation of the other lipoproteins with a polyanion/divalent cation mixture. Total cholesterol, triglyceride, and HDL cholesterol analyses were performed by the Hitachi 704 Analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). The plasma glucose concentration was measured by using an enzymatic reaction (Cobas Mira Chemistry System; Roche Diagnostic Systems, Montclair, NJ). LDL cholesterol concentration was calculated by the Friedewald equation as follows: LDL cholesterol = total cholesterol − HDL − triglyceride/5 for participants with a triglyceride concentration <400 mg/dl. C-reactive protein (CRP) was measured by using latex-enhanced nephelometry (Behring Diagnostics, Somerville, NJ).

Definition of metabolic syndrome. According to the National Cholesterol Education Program's Adult Treatment Panel III guidelines (15), men are considered to have metabolic syndrome if they have ≥3 of the following 5 criteria: *1*) abdominal obesity (waist circumference >102 cm), *2*) concentration of triglycerides ≥150 mg/dl (1.7 mmol/l), *3*) concentration of HDL cholesterol <40 mg/dl (1.02 mmol/l), *4*) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg), and *5*) fasting glucose level ≥100 mg/dl (5.6 mmol/l). In addition, individuals currently using prescribed medicine to treat hypertension are counted as having high blood pressure; those using antidiabetic medication (i.e., insulin or oral agents) are considered to have diabetes.

Fasting serum insulin and homeostasis model assessment of insulin resistance. Plasma insulin concentration was measured by using an insulin radioimmunoassay kit (Pharmacia Diagnostics, Uppsala, Sweden). The homeostasis model assessment (HOMA) has been shown to be a reliable estimate for insulin resistance (HOMA-IR) and is calculated as follows: HOMA-IR = (glucose [millimoles per liter] × insulin [microunits per milliliter])/22.5 (16). Concentrations of fasting insulin and HOMA-IR were transformed by natural logarithm to approximate normal distributions before they were analyzed in linear regression models.

Demographic, lifestyle, and behavioral covariates. Demographic covariates included age (in years) and race/ethnicity (i.e., white, African American, Mexican American, and other). Smoking status was determined as current smokers, former smokers (have smoked at least 100 cigarettes during their entire life but did not smoke at the interview), and never smokers. Alcohol intake was the sum of the frequencies of beer, wine, and hard liquor intake per month reported by participants. BMI was calculated by using mea-

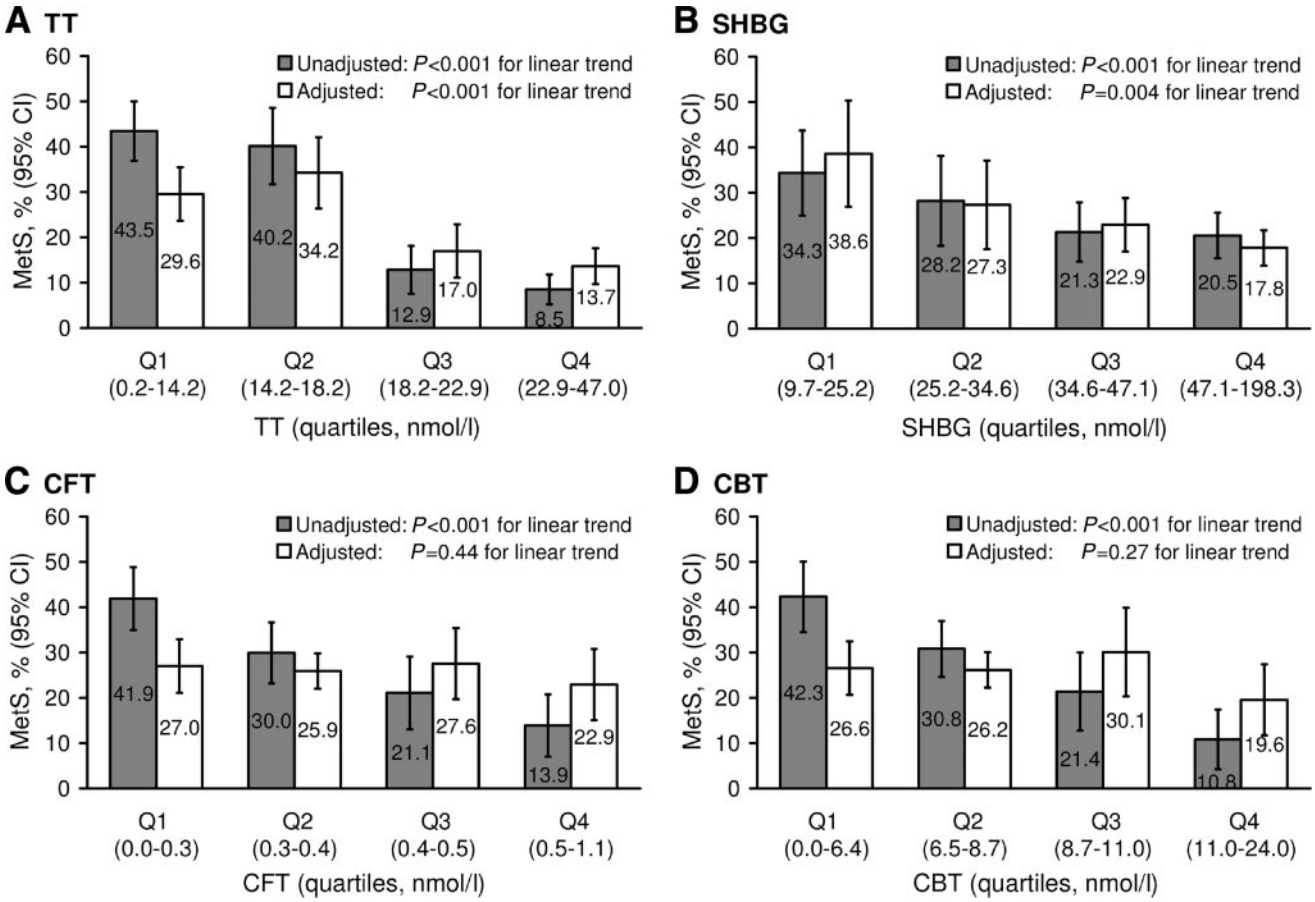

Figure 1—*Unadjusted and adjusted prevalence of the metabolic syndrome by quartiles for levels of total testosterone (TT) (A), SHBG (B), CFT (C), and CBT (D) in U.S. men ≥20 years of age, NHANES III, Phase I, 1988–1991. Covariates adjusted for were age, race, smoking status, alcohol intake, physical activity level, LDL cholesterol level, CRP level, and HOMO-IR. MetS, metabolic syndrome; Q, quartile.*

sured weight in kilograms divided by the square of height in meters. Physical activity level was determined by participants' self-reported frequency of engaging in specific types of leisure-time exercise or activities during the past month multiplied by the rate of energy expenditure (intensity rating) according to a standardized coding method (17).

Statistical analysis

First, we estimated mean concentrations of total testosterone, SHBG, CFT, and CBT by age and their correlations with the logarithmic values of fasting insulin concentration and HOMA-IR. Second, we estimated the adjusted mean concentrations of logarithmic values of fasting insulin and HOMA-IR in multivariable linear regression models and calculated the geometric means by taking the exponentiation of the adjusted means and their 95% CIs to facilitate interpretation of the results. Third, we estimated the unadjusted prevalence of metabolic syndrome by the quartiles of the four sex hormone measures. The quartiles of the sex hormone variables were determined according to the weighted distributions of their original values. Fourth, we estimated the prevalence ratios and 95% CI of metabolic syndrome for testosterones and SHBG as continuous variables and categorical variables using Cox proportional hazards models. The continuous testosterone and SHBG variables were transformed by natural logarithm and were standardized with the mean of 0 and SD of 1 to facilitate comparisons across the four sex hormone measures. The estimates for the association between sex hormones and metabolic syndrome were adjusted in three models: *1*) for age, *2*) for age and additional demographic characteristics and cardiovascular risk factors, and *3*) for HOMA-IR or fasting serum insulin concentration in addition to all covariates in *2*. Finally, we estimated the prevalence ratio and 95% CI of the sex hormones for the five single metabolic syndrome components.

The *t* test and χ^2 test were used to assess the differences in the mean values of continuous variables and the differences in the proportion of categorical variables for men with and without metabolic syndrome. Results with $P < 0.05$ were considered to be statistically significant for two-sided tests. All analyses were conducted with SUDAAN software (release 9.0; Research Triangle Institute, Research Triangle Park, NC) to account for the complex sampling design of NHANES III. All results were weighted to represent the U.S. population.

RESULTS — Fasting insulin (in a natural log scale) was significantly correlated with total testosterone ($r = -0.41$), SHBG ($r = -0.28$), CFT ($r = -0.22$), and CBT ($r = -0.24$) (all $P < 0.0001$). Similarly, HOMA-IR (in a natural log scale) was significantly correlated with total testosterone ($r = -0.42$), SHBG ($r = -0.25$), CFT ($r = -0.26$), and CBT ($r = -0.28$) (all $P < 0.0001$).

After adjustment for potential confounding effects, the geometric means of

Table 2—*Prevalence ratios and 95% CI of the metabolic syndrome (as defined by National Cholesterol Education Program Adult Treatment Panel III) by the quartiles of testosterones and SHBG in U.S. men ≥20 years of age, NHANES III Phase I, 1988–1991*

		Prevalence ratio (95% CI)		
	n	Model 1	Model 2	Model 3
Total testosterone (nmol/l)				
1 SD increase (log scale)	1,226	0.83 (0.76–0.91)	0.81 (0.73–0.89)	0.87 (0.80–0.94)
1st quartile (0.2–14.2)	351	3.77 (2.50–5.71)	3.99 (2.60–6.13)	2.16 (1.53–3.06)
2nd quartile (14.2–18.2)	308	3.99 (2.63–6.04)	4.11 (2.70–6.25)	2.51 (1.86–3.37)
3rd quartile (18.2–22.9)	289	1.37 (0.83–2.26)	1.37 (0.84–2.25)	1.24 (0.78–1.97)
4th quartile (22.9–47.0)	278	1.00 (referent)	1.00 (referent)	1.00 (referent)
P value†		<0.001	0.01	<0.001
SHBG (nmol/l)§				
1 SD increase (log scale)	1,226	0.57 (0.52–0.64)	0.58 (0.51–0.67)	0.71 (0.60–0.82)
1st quartile (9.7–25.2)	259	3.64 (2.48–5.35)	3.32 (2.12–5.20)	2.17 (1.32–3.56)
2nd quartile (25.2–34.6)	292	2.37 (1.47–3.84)	2.18 (1.37–3.49)	1.54 (0.95–2.48)
3rd quartile (34.6–47.1)	299	1.58 (1.01–2.45)	1.53 (0.99–2.36)	1.29 (0.82–2.02)
4th quartile (47.1–198.3)	376	1.00 (referent)	1.00 (referent)	1.00 (referent)
P value†		<0.001	<0.001	0.02
CFT (nmol/l)‡				
1 SD increase (log scale)	1,226	0.93 (0.84–1.04)	0.91 (0.82–1.02)	0.95 (0.85–1.07)
1st quartile (0.0–0.3)	397	1.76 (1.03–3.01)	1.77 (1.00–3.15)	1.18 (0.81–1.72)
2nd quartile (0.3–0.4)	279	1.61 (0.91–2.88)	1.54 (0.90–2.64)	1.13 (0.74–1.72)
3rd quartile (0.4–0.5)	255	1.39 (0.78–2.48)	1.41 (0.76–2.60)	1.20 (0.77–1.88)
4th quartile (0.5–1.1)	295	1.00 (referent)	1.00 (referent)	1.00 (referent)
P value†		0.03	0.05	0.45
CBT (nmol/l)‡				
1 SD increase (log scale)	1,226	0.93 (0.84–1.03)	0.92 (0.82–1.03)	0.97 (0.85–1.09)
1st quartile (0.0–6.4)	412	2.27 (1.23–4.20)	2.17 (1.08–4.35)	1.36 (0.87–2.13)
2nd quartile (6.5–8.7)	294	2.13 (1.03–4.41)	1.95 (0.96–3.95)	1.34 (0.78–2.29)
3rd quartile (8.7–11.0)	247	1.81 (0.95–3.47)	1.79 (0.89–3.61)	1.54 (0.95–2.49)
4th quartile (11.0–24.0)	273	1.00 (referent)	1.00 (referent)	1.00 (referent)
P value†		0.03	0.02	0.26

Model 1: adjusted for age only. Model 2: adjusted for age, race, smoking status, alcohol intake, physical activity, LDL cholesterol, and CRP. Model 3: adjusted for all covariates in model 2 and HOMA-IR. *To convert nanomoles per liter to nanograms per milliliter, divide by 3.4. †*P* values were estimated in the *t* test of deviation from linear trend for the prevalence of the metabolic syndrome. ‡Estimated according to the methods proposed by Vermeulen et al. (14).

fasting serum insulin decreased from the first (lowest) quartile to the fourth (highest) quartile of total testosterone ($P < 0.001$), SHBG ($P < 0.001$), CFT ($P = 0.02$), and CBT ($P = 0.02$) (Table 1). Similarly, the geometric means of the HOMA-IR decreased from the first quartile to the fourth quartile of total testosterone ($P < 0.001$), SHBG ($P < 0.001$), CFT ($P = 0.02$), and CBT ($P = 0.02$) (Table 1).

The unadjusted prevalence of metabolic syndrome steadily decreased from the first (lowest) quartile to the fourth (highest) quartile of all four sex hormone measures (all $P < 0.001$ for linear trend (Fig. 1). However, after adjustment for potential confounding effects, the significant linear trend in the prevalence of metabolic syndrome from lowest quartile to highest quartile remained only for total testosterone ($P < 0.001$) (Fig. 1*A*) and SHBG ($P = 0.004$) (Fig. 1*B*).

The associations between the continuous sex hormone indexes and metabolic syndrome are shown in Table 2. The results indicated that a 1 SD increase in the logarithmic value of total testosterone, SHBG, CFT, and CBT concentration was associated with ~17, ~43, ~7, and ~7% decreases in the prevalence of metabolic syndrome after adjustment for age (model 1). With Additional adjustment for race/ethnicity, smoking status, alcohol intake, physical activity level, LDL cholesterol, CRP, and HOMA-IR, the associations remained significant only for total testosterone and SHBG (model 2 and model 3).

The results of Cox regression models with testosterones and SHBG as categorical variables and with age adjustment (Table 2, model 1) showed a significant linear trend for the prevalence ratios of total testosterone ($P < 0.001$), SHBG ($P < 0.001$), CFT ($P = 0.03$), and CBT ($P = 0.03$) for metabolic syndrome. The age-adjusted prevalence ratios comparing the lowest quartile to the highest quartile (i.e., the referent group) ranged from 1.76 for CFT to 3.77 for total testosterone. After additional adjustment for race/ethnicity, smoking status, alcohol intake, physical activity level, LDL cholesterol, and CRP, the linear trend of the prevalence ratios remained statistically significant for total testosterone ($P = 0.01$), SHBG ($P < 0.001$), CFT ($P = 0.05$), and CBT ($P = 0.02$) (Table 2, model 2). However, after further adjustment for HOMA-IR (on the basis of model 2), the linear trend of the prevalence ratios was significant for only total testosterone ($P < 0.001$) and SHBG ($P = 0.02$) (Table 2, model 3). We replicated the analyses of model 3 in Table 2 by replacing HOMA-IR with fasting serum insulin and obtained similar results (data not shown).

Figure 2 shows the adjusted prevalence ratio and 95% CI of total testosterone, SHBG, CFT, and CBT for the five

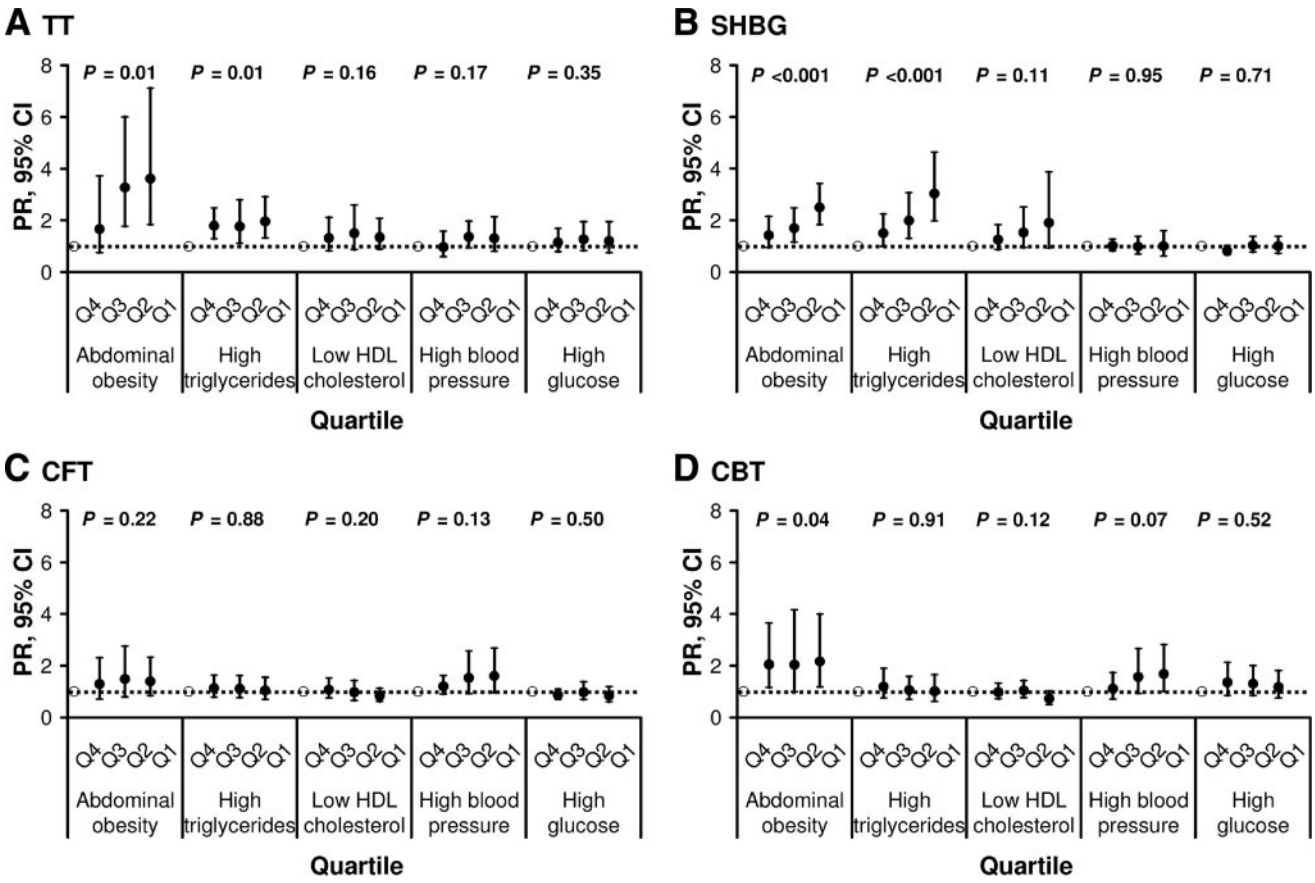

Figure 2—*Prevalence ratios (PRs) and 95% CI by quartiles of total testosterone (TT) (A), SHBG (B), CFT (C), and CBT (D) for the five single metabolic syndrome risk factors in U.S. men ≥20 years of age, NHANES III, Phase I, 1988–1991. Covariates adjusted for were age, race, smoking status, alcohol intake, physical activity level, LDL cholesterol level, CRP level, and HOMO-IR.* P *values were obtained in* t *tests for the linear trends of adjusted prevalence ratios.*

single metabolic syndrome components. Total testosterone was significantly associated with abdominal obesity ($P = 0.01$) and high concentrations of triglycerides ($P = 0.01$) (Fig. 2*A*). SHBG was also significantly associated with abdominal obesity ($P < 0.001$ for linear trend) and a high concentration of triglycerides ($P < 0.001$) (Fig. 2*B*). CFT was not significantly associated with any metabolic syndrome components ($P > 0.10$) (Fig. 2*C*). CBT was significantly associated with abdominal obesity ($P = 0.04$) and marginally associated with high blood pressure ($P = 0.07$) (Fig. 2*D*).

We replicated the analyses after exclusion of men with diagnosed diabetes ($n = 60$) and those with a fasting glucose concentration ≥126 mg/dl ($n = 77$). Estimates for the associations between sex hormones and metabolic syndrome were similar to that in the sample including those with diabetes (data not shown).

CONCLUSIONS — Our findings from this large representative sample of noninstitutionalized civilian adults in the U.S. indicated that men with lower concentrations of total testosterone and SHBG had a higher likelihood of having metabolic syndrome than those with higher concentrations. This finding was independent of traditional cardiovascular risk factors and surrogate measures of insulin resistance. Further, the effects of total testosterone and SHBG on metabolic syndrome seem to be more significant than those of CBT and CFT.

Because they are not bound to albumin and SHBG, researchers have hypothesized that free testosterone and CBT may be better indexes of biological activity than total testosterone alone (18). Our findings, however, do not support this "free hormone" hypothesis. In our study, total testosterone and SBHG, rather than CFT or CBT, were independently and strongly associated with metabolic syndrome. These findings are consistent with recent reports by others (10,11), in which total testosterone and SHBG were found to be significantly related to metabolic syndrome incidence or prevalence, whereas CFT was not. These population data highlight the independent and important role of SHBG in the pathogenesis of metabolic syndrome.

As with previous studies (5), we found that lower concentrations of total testosterone, SHBG, CFT, and CBT were significantly associated with higher levels of HOMA-IR and fasting serum insulin, two proxy biomarkers of insulin resistance. In particular, the strength of the association between sex hormones and metabolic syndrome decreased appreciably before and after adjustment for HOMA-IR, suggesting that insulin resistance may play a role in the observed association. A previous study has shown that insulin may directly inhibit SHBG secretion from hepatoma cells in vitro (19). In vivo studies show that insulin may stimulate testosterone production and reduce SHBG concentration in both normal-weight and obese men (20). However, polymorphisms in the SHBG gene have recently been shown to affect

not only SHBG levels but also type 2 diabetes risks, suggesting a potential causal role in the pathophysiological mechanisms. In particular, carriers of SHBG rs6257 allele (CC or CT) have an increased risk, whereas carriers, both men and women, of an rs6259 variant allele (AA or AG) have a decreased risk of type 2 diabetes (21). Furthermore, the association between low testosterone concentration and insulin resistance may be partially caused by impaired Leydig cell function (22).

Notably, total testosterone and SHBG were significantly associated with abdominal obesity and high triglyceride concentration among the five metabolic syndrome components. Although the exact mechanisms for the association remain unknown, observational studies have suggested that testosterone inhibits lipid uptake, decreases lipoprotein-lipase activity, and reduces visceral adipose tissue accumulation. In a randomized clinical trial, testosterone therapy selectively reduced visceral fat accumulation and increased fat-free mass (23). On the other hand, SHBG has been related to dyslipidemia, possibly by regulating hepatic lipoprotein lipase activity and reducing the release of fatty acids from adipocytes (24). Furthermore, recent clinical trials have shown that testosterone replacement therapy significantly reduces insulin resistance and improves glycemic control and cardiometabolic risk factors in hypogonadal men with type 2 diabetes (25).

Taken together, these findings may have significant implications in clinical practice. Because the total testosterone and SHBG were associated with metabolic syndrome independently of known cardiovascular risk factors, insulin resistance, and/or overall obesity, total testosterone and SHBG may be considered as emerging risk factors for metabolic syndrome in men. Conventionally, SHBG has not been considered as a risk factor in the development of any diseases (i.e., cancer, fracture, heart disease, and type 2 diabetes) because it has been viewed as a hormone sequester to control the bioavailability of steroids. Our results on the independent association of total testosterone and SHBG with metabolic syndrome suggest that SHBG may have important biological effects in a series of adverse metabolic outcomes.

The strengths of our study include the use of a large representative sample of U.S. adult men as well as rigorous and standardized assessment of biochemical analyses and anthropometric indexes in NHANES III. Our results, however, are subject to several limitations. First, using a cross-sectional design, we were unable to establish a temporal sequence in the associations among testosterones, SHBG, and metabolic syndrome. As shown in longitudinal studies, low total testosterone and SHBG concentrations predict the occurrence of metabolic syndrome (10,11). Conversely, individuals with diabetes and/or metabolic syndrome may be more likely to have hypogonadism, testosterone deficiency, or erectile dysfunction than those without. Second, we used calculated rather than directly measured free testosterone and bioavailable testosterone. However, previous studies have demonstrated that calculated free and bioavailable concentrations are valid and reliable (14). Third, surrogate measures of insulin resistance were used in our study. Direct measures of insulin resistance such as steady-state plasma glucose concentration or hyperinsulinemic-euglycemic clamp may be useful to reduce measurement errors.

Our results demonstrate that total testosterone and SHBG concentrations were strongly associated with metabolic syndrome independently of traditional cardiovascular risk factors and surrogate measures of insulin resistance. However, CFT and CBT concentrations were associated with metabolic syndrome but not independently of insulin resistance. Because metabolic syndrome and insulin resistance are risk factors for cardiovascular diseases and type 2 diabetes, early detection of men with decreased total testosterone and SHBG concentrations in clinical settings will be beneficial for preventing future cardiovascular outcomes.

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