Testosterone and Sex Hormone–Binding Globulin Predict the Metabolic Syndrome and Diabetes in Middle-Aged Men

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OBJECTIVE — In men, hypoandrogenism is associated with features of the metabolic syndrome, but the role of sex hormones in the pathogenesis of the metabolic syndrome and diabetes is not well understood. We assessed the association of low levels of testosterone and sex hormone–binding globulin (SHBG) with the development of the metabolic syndrome and diabetes in men.

RESEARCH DESIGN AND METHODS — Concentrations of SHBG and total and calculated free testosterone and factors related to insulin resistance were determined at baseline in 702 middle-aged Finnish men participating in a population-based cohort study. These men had neither diabetes nor the metabolic syndrome.

RESULTS — After 11 years of follow-up, 147 men had developed the metabolic syndrome (National Cholesterol Education Program criteria) and 57 men diabetes. Men with total testosterone, calculated free testosterone, and SHBG levels in the lower fourth had a severalfold increased risk of developing the metabolic syndrome (odds ratio [OR] 2.3, 95% CI 1.5–3.4; 1.7, 1.2–2.5; and 2.8, 1.9–4.1, respectively) and diabetes (2.3, 1.3–4.1; 1.7, 0.9–3.0; and 4.3, 2.4–7.7, respectively) after adjustment for age. Adjustment for potential confounders such as cardiovascular disease, smoking, alcohol intake, and socioeconomic status did not alter the associations. Factors related to insulin resistance attenuated the associations, but they remained significant, except for free testosterone.

CONCLUSIONS — Low total testosterone and SHBG levels independently predict development of the metabolic syndrome and diabetes in middle-aged men. Thus, hypoandrogenism is an early marker for disturbances in insulin and glucose metabolism that may progress to the metabolic syndrome or frank diabetes and may contribute to their pathogenesis.

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In cross-sectional studies, low levels of total and free testosterone and sex hormone–binding globulin (SHBG) in men have consistently been associated not only with type 2 diabetes, but also with visceral obesity, insulin resistance or hyperinsulinemia, dyslipidemia (1–7), and, more recently, the metabolic syndrome itself (6). The association of testosterone and SHBG with an altered lipid profile is partly secondary to abdominal fat accumulation, but there also appears to be an independent relationship between low levels of testosterone and hyperinsulinemia (4) and dyslipidemia (8). Low levels of testosterone have also predicted worsening abdominal obesity (9).

Testosterone itself may have a central or permissive role in the pathogenesis of the metabolic syndrome and type 2 diabetes by increasing skeletal muscle tissue and decreasing abdominal obesity and nonesterified fatty acids, consequently improving insulin sensitivity (10). Overall or abdominal obesity increases glucocorticoid turnover and production, which disturbs regulation of the hypothalamic-pituitary-adrenal axis (11,12) and may contribute to mild hypoandrogenism in men. An imbalance between levels of testosterone and its metabolite dihydrotestosterone could also contribute (13).

Orchiectomized rats show marked insulin resistance, confined to peripheral tissues, and these metabolic abnormalities are corrected by physiological doses of testosterone (14). In relatively small randomized controlled trials, androgen treatment has improved insulin sensitivity in middle-aged abdominally obese men (10,15), although findings have not been completely consistent (16). Diabetes or the metabolic syndrome as an end point has not been investigated.

Epidemiological evidence suggests that low levels of testosterone or SHBG may predispose to type 2 diabetes, but the few prospective nested case-control (17) or cohort (18,19) studies reported have not controlled adequately for potentially confounding factors such as fasting glucose and insulin levels (18,19), were not population-based (17,19), or used self-reported diabetes as an end point (18). No studies with the metabolic syndrome as an end point have to our knowledge been published. We therefore examined the role of total and free testosterone and SHBG in the prediction of the metabolic syndrome and diabetes in 702 middle-aged men who at baseline had neither the metabolic syndrome nor diabetes.

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Abbreviations: NCEP, National Cholesterol Education Program; SHBG, sex hormone–binding globulin; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

The subjects were participants of the Kuopio Ischemic Heart Disease Risk Factor Study, which is an ongoing prospective population-based study designed to investigate risk factors for chronic diseases, including type 2 diabetes and cardiovascular diseases, among middle-aged men (20). The study population was a random age-stratified sample of men living in Eastern Finland who were 42, 48, 54, or 60 years old at baseline examinations in 1987–1989, of whom 854 underwent repeat examination in 1998–2001. The Research Ethics Committee of the University of Kuopio and Kuopio University Hospital approved the study. All study subjects gave their written informed consent. The recruitment of the subjects has been previously described in detail (20). The present study included 702 men who at baseline did not have the metabolic syndrome or diabetes and who had complete data on sex hormones.

Anthropometric and biochemical measurements

BMI was computed as the ratio of weight to the square of height (kg/m^2). Waist girth was taken as the average of two measurements taken after inspiration and expiration at the midpoint between the lowest rib and the iliac crest. Waist-to-hip ratio (WHR) was defined as the ratio of waist girth to the circumference of the hips measured at the trochanter major.

Blood pressure was measured with a random zero mercury sphygmomanometer (Hawksley, West Sussex, U.K.). The measurement protocol included three measurements in supine, one in standing, and two in a sitting position with 5-min intervals. The mean of all six measurements was used as systolic and diastolic blood pressure.

Subjects were asked to fast for 12 h before blood sampling, which was done between 8:00 and 10:00 A.M. They were also asked to refrain from smoking for 12 h and from consuming alcohol for 3 days before blood draws. Blood glucose was measured using a glucose dehydrogenase method after precipitation of proteins by trichloroacetic acid. The serum samples for insulin determination were stored frozen at −80°C. Serum insulin was determined with a Novo Biolabs radioimmunoassay kit (Novo Nordisk, Bagsvaerd, Denmark). HDL fractions were separated from fresh serum by combined ultracentrifugation and precipitation. The cholesterol contents of lipoprotein fractions and serum triglycerides were measured enzymatically.

Measurement of sex hormones and SHBG

SHBG was determined using the 1235 AutoDELFIA automatic system based on a time-resolved fluoroimmunoassay (AutoDELFIA SHBG; Wallac, Turku, Finland). Total testosterone levels were measured with the AutoDELFIA Testosterone kit (Wallac). Non–SHBG-bound free testosterone (fT) was calculated as follows (21,22): proportion (%) of fT (fT%) = $2.28 - 1.38 \times \log(\text{SHBG nmol/l}/10)$, and serum fT (pmol/l) = fT% × T (nmol/l) × 10.

In this cohort, this formula has a correlation of $r = 0.998$ with that of Nanjee and Wheeler (23). Cutoffs for biochemical hypogonadism were defined as total testosterone <11 nmol/l or calculated free testosterone <160 pmol/l.

Definition of the metabolic syndrome and diabetes

The metabolic syndrome as defined by the National Cholesterol Education Program (NCEP) was three or more of the following: fasting blood glucose levels ≥5.6 mmol/l (equivalent to plasma glucose levels ≥6.1 mmol/l [24]), serum triglycerides ≥1.7 mmol/l, serum HDL <1.0 mmol/l, blood pressure ≥130/85 mmHg, and waist girth >102 cm (25). Diabetes at baseline and follow-up was defined as a fasting blood glucose concentration ≥6.1 mmol/l (equivalent to plasma glucose ≥7.0 mmol/l) or a clinical diagnosis of diabetes with treatment by diet, oral medications, or insulin (24).

Other assessments

Assessments of medical history and medications, smoking, alcohol consumption, adult socioeconomic status, and moderate-to-vigorous leisure-time physical activity have been described previously (26–28).

Statistical analysis

Differences in baseline clinical and biochemical characteristics between men who developed diabetes and those who did not were tested for statistical significance with the Student's *t* test and, where indicated, the χ^2 test. To assess the associations of testosterone and SHBG with diabetes, concentrations of testosterone and SHBG were dichotomized by the lower quartile and entered into logistic regression models adjusting for *1*) age; *2*) age, smoking, alcohol intake, adult socioeconomic status, leisure-time physical activity, and presence of cardiovascular disease; *3*) variables in model 2 and BMI; *4*) variables in model 2 and waist (for the metabolic syndrome) or WHR (for diabetes); *5*) concentrations of insulin, glucose, and triglycerides; and *6*) systolic blood pressure and use of blood pressure medication. Waist girth was used as a covariate in models with the metabolic syndrome as an end point and the WHR in models with diabetes as an end point, because these respective measures were stronger predictors than the other measures of obesity and fat distribution. Clinically used cutoffs for hypogonadism (total testosterone <11 nmol/l, calculated free testosterone <160 pmol/l) were similarly analyzed. To assess the association of low testosterone levels with a three-variable metabolic outcome (neither the metabolic syndrome nor diabetes, either the metabolic syndrome or diabetes, or both the metabolic syndrome and diabetes at the 11-year follow-up), polynomial logistic regression was used. The covariates for the logistic regression models were forced into the model.

Variables are given as means ± SD, except for variables with a skewed distribution (SHBG, insulin, triglycerides, physical activity), which are given as medians and interquartile ranges, and proportions, which are given as percentages. In analyses using continuous variables, these variables were log transformed. Statistical significance was considered to be $P < 0.05$. All statistical analyses were performed with SPSS 11.0 for Windows (SPSS, Chicago, IL).

RESULTS

Baseline clinical characteristics

Men who developed the metabolic syndrome or diabetes during the 11-year follow-up were heavier, had a larger waist and higher WHR, had higher glucose and insulin concentrations, and were more hypertensive and dyslipidemic at baseline (Table 1). Baseline concentrations of serum total and calculated free testosterone and SHBG were lower in men who developed the metabolic syndrome or diabetes

Table 1—*Baseline characteristics of the entire cohort, who did not have the metabolic syndrome or diabetes at baseline, and men who developed the metabolic syndrome or diabetes during follow-up*

	Entire cohort	Metabolic syndrome at follow-up	Diabetes at follow-up
n	702	147	57
Age (years)	51.3 ± 6.7	51.4 ± 6.8	52.2 ± 5.6
Smokers (%)	27	33*	21
Cardiovascular disease (%)	32	40*	35
Alcohol consumption (g/week)	32 (7–92)	42 (8–107)	42 (4–106)
Family history of diabetes (%)	26	31	37
Adult socioeconomic status score	7.2 ± 4.0	7.3 ± 4.0	7.1 ± 4.0
Systolic blood pressure (mmHg)	130 ± 15	134 ± 15‡	133 ± 14
Diastolic blood pressure (mmHg)	87 ± 8	90 ± 10‡	89 ± 10†
Blood pressure medication (%)	16	27‡	23
BMI (kg/m^2)	26.2 ± 2.9	28.1 ± 2.6‡	27.8 ± 2.7‡
WHR	0.93 ± 0.06	0.97 ± 0.07‡	0.97 ± 0.09‡
Waist circumference (cm)	88.7 ± 8.7	94.2 ± 6.6‡	94.1 ± 6.9‡
Serum LDL cholesterol (mmol/l)	3.8 ± 0.9	3.8 ± 0.9	3.8 ± 0.9
Serum HDL cholesterol (mmol/l)	1.32 ± 0.29	1.21 ± 0.20‡	1.29 ± 0.21
Serum triglycerides (mmol/l)	1.11 (0.82–1.58)	1.42 (1.05–1.82)‡	1.45 (1.05–1.71)‡
Fasting blood glucose (mmol/l)	4.49 ± 0.43	4.61 ± 0.45‡	4.87 ± 0.46‡
Fasting serum insulin (mU/l)	8.8 (6.7–11.3)	10.9 (8.1–14.0)‡	12.1 (7.9–16.1)‡
Moderate and vigorous leisure-time physical activity (min/week)	1.34 (57–241)	128 (45–218)	107 (32–240)
Serum total testosterone (nmol/l)	20.4 ± 6.9	18.3 ± 6.4‡	18.0 ± 6.6†
Low testosterone levels (<11 nmol/l)	5%	7%	11%*
Calculated free testosterone (pmol/l)	304 ± 75	291 ± 79*	286 ± 71
Low free testosterone (<160 pmol/l)	1.4%	1.4%	3.5%
SHBG (nmol/l)	34.5 (26.3–43.9)	28.2 (23.3–38.1)‡	26.2 (22.2–38.3)†

Data are means ± SD, medians (interquartile range), or percent. Higher adult socioeconomic status score means lower socioeconomic status. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$, univariate logistic regression analysis with either the metabolic syndrome or diabetes as the outcome variable.

during follow-up, but for calculated free testosterone, the difference was statistically significant only for men who developed the metabolic syndrome. Men who developed diabetes more often had hypogonadism as defined by low total testosterone levels, but the proportion of men with hypogonadism, as defined by calculated free testosterone levels, did not differ between men who developed or did not develop diabetes.

Testosterone, SHBG, and development of the metabolic syndrome and diabetes

After adjustment for age, men with concentrations of total testosterone, calculated free testosterone, or SHBG in the lower fourth were 1.7–2.8 times more likely to develop the metabolic syndrome than other men during the 11-year follow-up (Table 2). Adjustment for potentially confounding factors such as smoking, alcohol intake, socioeconomic status, cardiovascular disease, and amount of moderate- or vigorous-intensity leisure-time physical activity (model 2) had little effect on the association. After further adjustment for BMI, the predictive value of low testosterone and SHBG concentrations was attenuated. After further adjustment for features related to insulin resistance (model 4), new cases of the metabolic syndrome were still 1.7-fold more common in men with low levels of total testosterone and SHBG, but the association of calculated free testosterone levels only tended to be significant. Other significant predictors of the metabolic syndrome were triglycerides (e.g., for the model with total testosterone, for a 1-SD log change, odds ratio [OR] 3.3, 95% CI 2.0–5.4), waist (1-SD change, 2.2, 1.7–2.8), systolic blood pressure (1-SD change, 1.3, 1.0–1.6), blood glucose (1-SD change, 1.3, 1.0–1.6), and smoking (≥20 cigarettes/day versus none, 2.3, 1.2–4.3). The association of insulin concentrations with subsequent development of the metabolic syndrome was not significant in model 4 but became significant when omitting waist circumference from the model (not shown). The presence or absence of testosterone or SHBG concentrations in the model did not materially influence the association of insulin or the other variables with development of the metabolic syndrome. The association of hypogonadism as defined by total testosterone <11 nmol/l or calculated free testosterone <160 pmol/l with the development of the metabolic syndrome was not significant.

Likewise, adjusting for age concentrations of total testosterone, calculated free testosterone, or SHBG in the lower fourth increased the risk of incident diabetes by 1.7- to 4.3-fold, although the association with calculated free testosterone did not reach statistical significance (Table 2). Adjusting for potentially confounding factors (model 2) had little effect on the association. After further adjustment for BMI (model 3) or for other features related to the metabolic syndrome (model 4), the associations were attenuated. Other significant predictors of incident diabetes were blood glucose (e.g., for the

Table 2—*ORs for developing the metabolic syndrome or diabetes during the 11-year follow-up for men in the lowest fourth of concentrations of serum total and calculated free testosterone and SHBG at baseline in 702 men initially without the metabolic syndrome or diabetes*

	Total testosterone (<15.6 nmol/l)	Calculated free testosterone (<253 pmol/l)	SHBG (<28.3 nmol/l)
Metabolic syndrome at the 11-year follow-up (*n/N* = 147/702)			
Model 1	2.28 (1.54–3.38)	1.71 (1.15–2.54)	2.78 (1.88–4.12)
Model 2	2.54 (1.69–3.81)	1.91 (1.27–2.89)	2.89 (1.93–4.33)
Model 3	1.92 (1.24–1.96)	1.58 (1.01–2.47)	2.18 (1.42–3.36)
Model 4	1.70 (1.07–2.70)	1.57 (0.98–2.50)	1.67 (1.05–2.65)
Diabetes at the 11-year follow up (*n/N* = 57/702)			
Model 1	2.33 (1.32–4.11)	1.66 (0.93–2.96)	4.34 (2.45–7.70)
Model 2	2.37 (1.32–4.24)	1.67 (0.91–3.05)	4.33 (2.41–7.77)
Model 3	1.95 (1.08–3.55)	1.42 (0.77–2.62)	3.60 (1.98–6.55)
Model 4	1.97 (1.03–3.77)	1.56 (0.80–3.06)	2.74 (1.42–5.29)

Data are ORs (95% CI). Model 1: age-adjusted. Model 2: adjusted for age, presence of cardiovascular disease, smoking (none, 1–19 cigarettes/day, ≥20 cigarettes/day), alcohol consumption (none and four levels of alcohol intake), and socioeconomic status. Model 3: adjusted for the variables in model 2 and BMI. Model 4: adjusted for the variables in model 2 and age; waist (for the metabolic syndrome) or WHR (for diabetes); concentrations of insulin, glucose, and triglycerides; and systolic blood pressure and use of blood pressure medication.

model with total testosterone, for a 1-SD change, OR 7.8, 95% CI 3.6–16), WHR (1-SD change, 1.6, 1.1–2.2), triglycerides (1-SD change, 2.2, 1.1–4.4), and insulin (1-SD log change, 2.3, 1.0–5.5). The association of hypogonadism as defined by total testosterone <11 nmol/l with incident diabetes was qualitatively similar as that for total testosterone dichotomized by the lower quartile when using the models shown in Table 2 (model 2, OR 2.94, 95% CI 1.11–7.75; model 3, 2.40, 0.89–6.44; model 4, 2.70, 0.92–7.91), although the association only tended to be significant for models 3 and 4. The association of hypogonadism as defined by calculated free testosterone <160 pmol/l with incident diabetes was not significant (not shown).

We also examined the association of low total testosterone levels at baseline with the metabolic outcome at the 11-year follow-up (neither the metabolic syndrome nor diabetes, either the metabolic syndrome or diabetes, or both the metabolic syndrome and diabetes; Fig. 1). In these analyses, low total testosterone levels at baseline were associated with a worse outcome at 11 years. Men who developed both the metabolic syndrome and diabetes were especially likely to have had low testosterone levels already at baseline.

CONCLUSIONS — This is the first study to show that total testosterone and SHBG concentrations in the low-normal range predict not only diabetes, but also the development of the metabolic syndrome as defined by the NCEP in middle-aged men, independently of BMI and other factors related to insulin resistance. Calculated free testosterone levels likewise predicted the metabolic syndrome, but not independently of BMI.

Men with total testosterone levels in the lower fourth were 2.3-fold more likely to develop the metabolic syndrome or diabetes than other men. Importantly, the increase in likelihood was nearly two times greater even after adjusting for baseline abdominal obesity and insulin and glucose levels in addition to other factors related to insulin resistance. Accordingly, men with hypogonadism based on a total testosterone concentration <11 nmol/l had an increased risk for incident diabetes. A few previous studies have assessed the prospective association of testosterone with the incidence of type 2 diabetes (17–19). In a prospective nested case-control study from the Multiple Risk Factor Intervention Trial, total and free testosterone levels were lower in the 176 men who developed diabetes than in the 176 control men (17). Even after matching for fasting glucose levels and BMI, free testosterone, but not total testosterone, was still associated with incident diabetes in multivariate models including glucose, BMI, and insulin (17). In that study, free testosterone concentrations were measured with a double antibody system instead of equilibrium dialysis. This antibody method may be influenced by SHBG concentrations (29). In a Massachusetts population-based study, low levels of centrifugal ultrafiltration-measured free testosterone, but not total testosterone, were determinants of incident type 2 diabetes 7–10 years later in 1,156 men independently of BMI and the presence of hypertension and cardiovascular disease (18). However, diabetes was diagnosed based on self-report or the use of insulin, and glucose and insulin levels were not

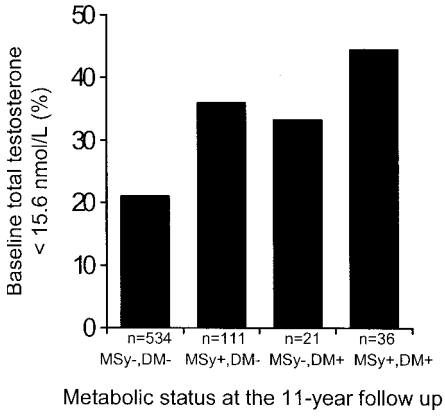

Figure 1—*Percentage of men with total testosterone levels at baseline in the lowest fourth (<15.6 nmol/l) according to metabolic status at the 11-year follow-up. DM, diabetes; MSy, metabolic syndrome.* P = *0.005 for the overall association of baseline testosterone levels <15.6 nmol/l with the metabolic status (neither the metabolic syndrome nor diabetes, either the metabolic syndrome or diabetes, or both the metabolic syndrome and diabetes) at the 11-year follow-up after adjustment for age and baseline cardiovascular disease, smoking, alcohol intake, socioeconomic status, WHR, insulin and glucose concentrations, triglyceride levels, systolic blood pressure, and blood pressure medication.*

measured. In 294 middle-aged and elderly men, total testosterone levels were lower in the 26 men who developed diabetes during the 8-year follow-up, but adjustment was made for only age, BMI, and systolic blood pressure (19). To our knowledge, the association of testosterone levels with the metabolic syndrome as defined by the NCEP has not been previously reported.

Testosterone itself may contribute to the pathogenesis of insulin resistance and diabetes by increasing skeletal muscle mass at the expense of fat mass and decreasing abdominal obesity through inhibition of lipoprotein lipase activity (10). Low levels of free or total testosterone have been consistently associated with overall or abdominal obesity, insulin resistance or hyperinsulinemia, hyperglycemia, and dyslipidemia (1–7). The associations have in some studies persisted even after adjustment for adiposity (4,6,8). Furthermore, low testosterone levels have predicted an increase in visceral fat during follow-up (9).

On the other hand, overall or abdominal obesity may decrease free and total testosterone levels. Consistent with abdominal or overall obesity playing a contributing role, we found that the association of free testosterone with diabetes was abolished and the association of total testosterone attenuated after adjustment for BMI, WHR, and other factors related to insulin resistance. The effect of weight loss on free and total testosterone and SHBG has been inconsistent, but overall or abdominal obesity increases glucocorticoid turnover and production (11,12), resulting in abnormal control of hypothalamic-pituitary-adrenal axis and possibly mild hypoandrogenism in men. Furthermore, obesity is associated with abnormally increased expression and activity of enzyme 11β-hydroxysteroid dehydogenase type 1 in adipose tissue (30–32). 11β-Hydroxysteroid dehydogenase type 1 determines local glucocorticoid concentrations through interconversion of cortisol and its inactive counterpart cortisone.

In multivariate analyses including BMI, calculated free testosterone did not predict development of the metabolic syndrome or diabetes, although our study is underpowered to rule out a small increase in risk with mildly decreased free testosterone levels. These findings agree with previous studies (18). Because total testosterone is also a function of SHBG, it may be that SHBG may be more important than testosterone itself, either as a risk marker for or as a contributor to the development of the metabolic syndrome or diabetes.

SHBG has been previously shown to be inversely related to components related to insulin resistance (3,5). Low SHBG concentrations have also predicted development of diabetes (18). Inhibition of insulin secretion by diazoxide leads to increased SHBG levels (33), suggesting that SHBG production in the liver is regulated by insulin. Furthermore, in cell cultures, insulin inhibits, whereas testosterone stimulates, SHBG production (34). Androgens may also mediate some of their effects through SHBG bound to the SHBG receptor (35). Regardless of the mechanism, SHBG seems at the very least to be a good risk marker for the metabolic syndrome or diabetes.

Our findings raise the following question: Can lifestyle or pharmacological intervention in overweight men at risk for type 2 diabetes and who have relatively low testosterone levels prevent or delay development of the metabolic syndrome or diabetes? We (36) and others (37) have found that weight loss and successful weight maintenance increase free and total testosterone and SHBG in men with general obesity (37) or abdominal obesity and the metabolic syndrome (36). Although effects on sex hormones were not reported, recent evidence from the Finnish Diabetes Prevention Study and U.S. Diabetes Prevention Program suggest that even relatively modest lifestyle interventions can have a major impact in decreasing the risk for diabetes in glucose-intolerant individuals (38,39). Furthermore, some studies have found that administration of testosterone improves insulin sensitivity, possibly via improvements in body composition and a reduction in circulating nonesterified fatty acids (10,15).

The strengths of this study include its large population-based design and detailed assessment of features related to insulin resistance. We calculated free testosterone levels rather than directly determining bioavailable testosterone, but calculation of free testosterone from total testosterone and SHBG seems to be valid in healthy individuals and in several pathological conditions (22,29).

Low total testosterone and SHBG levels predict development of the metabolic syndrome and diabetes in middle-aged men, independently of other factors related to insulin resistance. Calculated free testosterone concentrations also identify men at risk for the metabolic syndrome, but not independently of obesity or insulin resistance. Thus, hypoandrogenism is an early marker for disturbances in insulin and glucose metabolism that may progress to the metabolic syndrome and frank diabetes and may contribute to their pathogeneses.

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