Testosterone, Sex Hormone–Binding Globulin, and the Development of Type 2 Diabetes in Middle-Aged Men

Prospective results from the Massachusetts Male Aging Study

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OBJECTIVE — The objective was to examine prospectively the association between low testosterone and sex hormone–binding globulin (SHBG) levels and the subsequent development of type 2 diabetes in men.

RESEARCH DESIGN AND METHODS — Analyses were conducted on the cohort of the Massachusetts Male Aging Study, a population-based random sample of men aged 40–70. Of the 1,709 men enrolled in 1987–1989 (T_1), 1,156 were followed up 7–10 years later (T_2). Testosterone and SHBG levels at T_1 were used to predict new cases of diabetes between T_1 and T_2.

RESULTS — After controlling for potential confounders, diabetes at follow-up was predicted jointly and independently by lower baseline levels of free testosterone and SHBG. The odds ratio for future diabetes was 1.58 for a decrease of 1SD in free testosterone (4 ng/dl) and 1.89 for a 1SD decrease in SHBG (16 nmol/l), both significant at $P < 0.02$.

CONCLUSIONS — Our prospective findings are consistent with previous, mainly cross-sectional reports, suggesting that low levels of testosterone and SHBG play some role in the development of insulin resistance and subsequent type 2 diabetes.

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Aging is associated with a decline in insulin action (1,2) and increasing prevalence of type 2 diabetes (3). In a large sample of healthy subjects, the European Group for Insulin Resistance demonstrated that insulin-mediated glucose disposal declines with advancing age. This is partially a consequence of changes toward obesity and central body-fat distribution (4).

In numerous cross-sectional studies, levels of testosterone in men have been inversely associated with several recognized risk factors for the development of type 2 diabetes, such as obesity (5), central adiposity (6–11), and an elevated fasting plasma concentration of insulin (7–9,12–14) and glucose (5,9,12). Two recent prospective studies found that low levels of testosterone and sex hormone–binding globulin (SHBG) predict the subsequent development of type 2 diabetes among aging men (15,16), and a small study suggested that hyperinsulinemia reduced SHBG concentrations among women with polycystic ovary syndrome (17). Low plasma testosterone concentration is associated with other correlates of diabetes, such as cardiovascular disease (18) and hypertension (5). It is not known whether the observed relationship between low plasma testosterone and diabetes is direct or indirect, because the relationship between testosterone and plasma insulin concentration is not fully understood.

Insulin is thought to regulate testosterone secretion, because inhibition of insulin secretion by long-term diazoxide treatment has been shown to decrease total and free testosterone and increase SHBG concentration in normal weight and obese healthy individuals (19). Conversely, testosterone administration to obese men has been shown to improve insulin sensitivity (20,21). SHBG has also been positively associated with insulin sensitivity (22) and negatively correlated with insulin resistance (9) and with plasma insulin (7,8) and glucose (8) levels.

Limited data exist linking testosterone and SHBG levels to insulin resistance or to the development of type 2 diabetes. Although several studies have reported lower levels of testosterone (6,13,23,24) and SHBG (13,24) among men with type 2 diabetes, the cross-sectional nature of those studies prevented examination of the direction of causality. Previous studies have also been limited by small sample size (20,21), nonrepresentative samples (16), and a restricted age range (15).

To further examine the association between low testosterone levels and the subsequent development of type 2 diabetes in men, we analyzed longitudinal data from a large population-based study of normally aging men.

RESEARCH DESIGN AND METHODS

— Subjects were participants in the Massachusetts Male Aging Study (MMAS), a longitudinal study of men randomly selected from Massachusetts city and town street lists. The study has been previously described in detail (25,26). Eligibility criteria for MMAS required that each

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Abbreviations: CV, coefficient of variation; MMAS, Massachusetts Male Aging Study; OR, odds ratio; SHBG, sex hormone–binding globulin; T_1, baseline interview; T_2, follow-up interview.

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

Table 1—*Characteristics of a population-based sample of 1,096 men from Massachusetts aged 40–70 years*

Characteristic	*n* (%)	Mean ± SD	Range
New diabetes diagnosis at T_2	54 (4.9)		
Total testosterone (ng/dl)	—	524 ± 172	34–1,352
Free testosterone (ng/dl)	—	9.9 ± 3.9	0.6–24.4
SHBG (nmol/l)	—	31.8 ± 15.8	6–170
Hypogonadism*	43 (4.0)	—	—
Age (years)	—	53.9 ± 8.3	40–70
Race			
Caucasian	1,067 (97.4)	—	—
African-American	16 (1.5)	—	—
Asian	8 (0.7)	—	—
Other	4 (0.4)	—	—
Hypertension	274 (25.0)	—	—
Heart disease	107 (9.8)	—	—
Physical activity			
None	64 (5.8)	—	—
Light (<200 kcal/day)	287 (26.2)	—	—
Moderate to intense (≥200 kcal/day)	744 (67.9)	—	—
Alcohol intake			
None	161 (14.7)	—	—
Light (≤3 drinks/day)	725 (66.1)	—	—
Moderate to heavy (>3 drinks/day)	210 (19.2)	—	—
Depression (CES-D ≥16)	97 (9.0)	—	—
Dominance (Jackson scale)	—	10.3 ± 3.9	0–16
BMI (kg/m^2)	—	27.1 ± 4.1	17.5–50.0
Erectile dysfunction			
None	630 (59.6)	—	—
Minimal	253 (23.9)	—	—
Moderate	85 (8.0)	—	—
Complete	89 (8.4)	—	—

Data are from 1987 to 1989 with a 9-year follow-up. *Total testosterone <250 ng/dl. CES-D, Center for Epidemiologic Studies Depression Scale.

subject be aged 40–70 years at the time of interview, living at the listed address, and not institutionalized or too ill to give the interview. The baseline interview (T_1) was conducted between 1987 and 1989 with 1,709 men, 53% of the eligible subjects contacted. The follow-up interview (T_2), conducted between 1995 and 1997, was completed with 1,156 members of the original cohort, comprising 76% of the survivors living in the U.S. The median interval between baseline and follow-up interviews for a given subject was 8.9 years. Reflecting the population of Massachusetts in 1990, the baseline sample was primarily Caucasian (95%), with a small number self-categorized as African-American (3%), Asian (1%), or other (1%).

All data-collection procedures were approved by the appropriate institutional review boards. The protocol was conducted in the subject's home by a trained interviewer/phlebotomist who obtained written informed consent. The interview consisted of a comprehensive interviewer-administered health questionnaire, an inventory of current medications, body measurements, a nonfasting blood sample, and a privately self-administered sexual activity questionnaire. To control for diurnal variation of hormone levels, blood was drawn within 4 h of the subject's awakening. Two samples were drawn 30 min apart to decrease variability from pulsatile secretion (27). The samples were frozen and later pooled for analysis at the laboratory of Dr. C. Longcope (University of Massachusetts Medical Center, Worcester, MA).

The outcome variable for this analysis was a new diagnosis of diabetes between T_1 and T_2. Diabetes was defined by either use of insulin or oral hypoglycemic agents or a positive response to the question, "Have you ever been told by a health professional that you have diabetes?" Self-report of diabetes has been shown to be relatively accurate (28). To limit the data to incident (new) cases at T_2, men with diabetes at T_1 were excluded from all analyses.

The predictors of primary interest were T_1 levels of testosterone and SHBG. Total testosterone was measured by radioimmunoassay (Diagnostic Products, Los Angeles, CA), with an interassay coefficient of variation (CV) of 7.2% and an intra-assay CV of 4.6%. The percentage of free testosterone was measured by centrifugal ultrafiltration (29) with an interassay CV of 7.1% and an intra-assay CV of 6.0%. The absolute level of free testosterone was calculated by multiplying total concentration by the percentage of free testosterone. SHBG was measured by a filtration assay (29) with an interassay CV of 10.9% and an intra-assay CV of 8.0%. Men with prostate cancer at T_1 were excluded from analysis because the disease or treatment might have affected testosterone levels (30).

Other potential predictors of diabetes were also measured at T_1. Self-reported history of hypertension and heart disease were ascertained as part of the health interview. Level of physical activity was estimated by recall of the past week's activities, including duration and intensity. The subject's average daily energy expenditure was categorized as "moderate/intense" (≥200 kcal/day), "light" (<200 kcal/day), or none (31). Alcohol intake was estimated from self-report of beer, wine, and liquor consumption, accounting for ethanol content, quantity, frequency, and concentrated periods of drinking according to the Khavari and Farber formula (32), with one "drink" defined as 12 g ethanol. Depression was measured with the Center for Epidemiologic Studies Depression Scale, with men scoring ≥16 considered depressed (33). Dominance was measured by a subscale of the Jackson Personality Research Form E (34). Height and weight were measured using standardized methods for large epidemiologic studies (35), and BMI was calculated as weight÷height^2. Erectile dysfunction was assessed by a formula combining 13 items from the self-administered sexual activity questionnaire (36).

Bivariate relations between incident diabetes and potential predictors were evaluated using Fisher's exact test for categorical variables and Student's *t* test for continuous variables. To assess the relative importance of testosterone, SHBG, and other variables in the development of diabetes, we constructed a multiple logistic

Table 2—*Unadjusted associations between incident diabetes and potential predictors in a population-based sample of men from Massachusetts aged 40–70 years*

Predictor	Diabetes	No diabetes	*P**
Total testosterone (ng/dl)	438 ± 26	529 ± 5	<0.001
Free testosterone (ng/dl)	8.3 ± 0.5	10.0 ± 0.1	0.004
SHBG (nmol/l)	24.4 ± 1.4	32.3 ± 0.5	<0.001
Hypogonadism†	15.1	3.3	<0.001
Age (years)	55.6 ± 1.2	53.8 ± 0.3	0.14
Hypertension	48.1	23.8	<0.001
Heart disease	20.4	9.2	0.015
Physical activity			
None	11.1	5.6	0.24
Light (<200 kcal/day)	24.1	26.4	
Moderate to intense (≥200 kcal/day)	64.8	68.0	
Alcohol intake			
None	20.4	14.3	0.44
Light (≤3 drinks/day)	63.0	66.3	
Moderate to heavy (>3 drinks/day)	16.7	19.3	
Depression	18.9	8.5	0.02
Dominance (Jackson scale)	9.3 ± 0.6	10.4 ± 0.1	0.05
BMI (kg/m^2)	31.0 ± 0.8	26.9 ± 0.1	<0.001
Erectile dysfunction, moderate/complete	20.8	16.3	0.45

Data are from 1987 to 1989 with a 9-year follow-up and are means ± SEM or %. *Testing equal mean (by Student's *t* test) or equal percentage (by Fisher's exact test) in men with and without incidence diabetes at T_2; †total testosterone <250 ng/dl.

regression model with incident diabetes as the dichotomous dependent variable. The model included all statistically significant predictors of incident diabetes from Table 2 ($P < 0.05$). We constructed several variants of the regression model using combinations of free testosterone, total testosterone, and SHBG—singly, in pairs, all three, or none—and used likelihood ratio tests (ΔG^2) to determine which hormone levels were necessary and sufficient for the best-fitting predictive model.

Of the 1,156 men in the follow-up sample, we excluded 61 because of baseline status (59 with diabetes, 2 with prostate cancer) and obtained an analysis sample of 1,096 men, of whom 1,030 had complete data for the outcome and all predictors used in multiple regression analysis.

RESULTS — Table 1 displays relevant characteristics of the sample. There were 54 men in the analysis sample (5%) who had a new diagnosis of diabetes between T_1 and T_2. At baseline, 43 men (4%) were hypogonadal, as defined by total testosterone <250 ng/dl. Hypertension was reported by 274 men at baseline (25%) and heart disease by 107 (10%).

Unadjusted associations between potential risk factors and subsequent development of diabetes are shown in Table 2. The mean testosterone level was significantly lower among men who later developed diabetes, as were mean levels of free testosterone and SHBG. The baseline age in the two groups was not significantly different. Other baseline variables significantly associated with subsequent development of diabetes were hypertension, heart disease, higher BMI, and depression. Dominance, though near significant in bivariate analysis, lost significance when tested in multiple regression and was dropped from further use.

The best-fitting multiple logistic regression for incident diabetes is displayed in Table 3. The Hosmer-Lemeshow goodness-of-fit statistic (37) indicated that the logistic model fit well ($P = 0.16$). After controlling for all other factors in the model, lower levels of free testosterone and SHBG jointly and independently predicted incident diabetes. The odds ratio (OR) in favor of incident diabetes was 1.58 for a decrease of 1SD in free testosterone (3.9 ng/dl), with 95% CI 1.08–2.29, significantly different from a null effect (OR = 1) with $P = 0.017$. The OR for diabetes was 1.89 for a 1SD decrease in SHBG level (15.8 nmol/l), with 95% CI 1.14–3.14, significant at $P = 0.014$.

Men with hypertension had significantly elevated likelihood of developing diabetes (OR 2.18) after controlling for other factors. Also remaining statistically significant in multiple regression were depression (OR 3.09) and BMI (OR 1.83 per SD). Heart disease carried an estimated OR of 1.96 for incident diabetes but lost statistical significance ($P = 0.11$) when we controlled for the other factors.

The mutual correlation among total testosterone, free testosterone, and SHBG obviated the need for all three variables in multiple regression. When total testosterone was added to the model shown in Table 3, it failed to make a significant contribution ($\Delta G^2 = 0.17$, $P = 0.68$), while free testosterone and SHBG retained their significance. We also found that total testosterone could not be substituted for free testosterone without harming the statistical fit ($\Delta G^2 = 4.43$, $P = 0.036$). Total testosterone was correlated with both free testosterone ($r = 0.71$, $P < 0.001$, free testosterone being a component of the total) and SHBG ($r = 0.30$, $P < 0.001$, the bulk of serum testosterone being bound to SHBG). By contrast, free testosterone and SHBG were virtually uncorrelated ($r = 0.04$, $P = 0.24$). Thus, the model shown in Table 3 appears to be the

Table 3—*Logistic regression analysis predicting incident diabetes in a population-based sample of men from Massachusetts aged 40–70 years*

Predictor	Increment	OR*	95% CI	*P*
Free testosterone	−1SD (3.9 ng/dl)	1.58	1.08–2.29	0.017
SHBG	−1SD (15.8 nmol/l)	1.89	1.14–3.14	0.014
Hypertension	Presence	2.18	1.14–4.15	0.018
Heart disease	Presence	1.96	0.85–4.50	0.11
Depression	Presence	3.09	1.34–7.12	0.008
BMI	+1SD (4.0 kg/m^2)	1.83	1.40–2.39	<0.001

Data are from 1987 to 1989 with a 9-year follow-up. *OR in favor of incident diabetes, given indicated increment in predictor. 95% CI from maximum-likelihood logistic model. *P* tests OR = 1.

best fitting and most informative, with free testosterone and SHBG each contributing predictive ability beyond the information given by other factors.

CONCLUSIONS — Type 2 diabetes is typically characterized by age dependence and insulin resistance (38). Consistent with previous studies, the current study showed unadjusted associations between type 2 diabetes and both low testosterone (6,13,15,16,23,24) and low SHBG (13,15,16,24) in aging men. Controversy remains regarding which of these levels is an independent predictor for the development of type 2 diabetes. As in our study, Haffner et al. (16) reported retrospective associations of diabetes with SHBG and free testosterone but not with total testosterone; conversely, Tibblin et al. (15) found an independent association for testosterone but only a marginally significant association for SHBG.

Regarding the relationship between insulin resistance and SHBG, it has been documented that both insulin and insulin-like growth factor 1 have inhibitory effects on SHBG secretion by Hep G2 cells in vitro (38). Insulin also suppresses hepatic SHBG synthesis (39). Thus, it has been proposed that SHBG levels could be a valuable marker of insulin resistance or hyperinsulinemia in humans (39).

The cross-sectional nature of previous studies has also led to some disagreement over the direction of causality in the relationship between sex hormones and diabetes in men. The results of the present study are consistent with other reports that low levels of SHBG and testosterone play a role in the development of insulin resistance and subsequently the development of type 2 diabetes. The independent predictive ability of SHBG, especially, needs further investigation.

Although the present study enabled us to examine the relationship between endogenous hormone levels and diabetes in a large group of normally aging men, our data have some obvious limitations. The population sampled was overwhelmingly white, and therefore race could not be examined as a potential confounder. We were unable to control simultaneously for obesity and body-fat distribution, because BMI and waist-to-hip ratio were too highly collinear to use in the same model. Of the two variables, BMI was chosen because it was more strongly related to incident diabetes.

The most important limitation was that insulin and glucose concentrations were not available in the baseline MMAS. The reliance on self-report of diabetes and medication use raises the possibility that some undetected type 2 or type 1 diabetic cases were included in the sample, although the latter are unlikely because of the age of the group examined. Because such misclassification is a bias toward the null, our positive findings are not compromised. Still, our inability to rule out existing glucose intolerance may explain the apparent predictive ability of hypertension, and it leaves open the possibility that elevated insulin was the cause of low SHBG rather than the reverse.

In summary, using prospective data from a large sample of normally aging men, we demonstrated a predictive relation, previously established only cross-sectionally, between low levels of free testosterone and SHBG and the incidence of type 2 diabetes in a large population-based random sample of aging men. By using multiple logistic regression to control for confounding effects of hypertension, obesity, and other covariates, we ensured that the observed predictive relationship was not attributable to those other factors. Low SHBG, in particular, appears to be a strong independent predictor for the development of type 2 diabetes, carrying additional predictive ability beyond that of testosterone alone. Low levels of SHBG and testosterone appear to play some role in the development of insulin resistance and the subsequent appearance of type 2 diabetes.

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