Sex Hormone–Binding Globulin and Glucose Tolerance in Postmenopausal Women

The Rancho Bernardo Study

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OBJECTIVE — Sex hormone–binding globulin (SHBG) has been shown to be associated with several diabetes risk factors, including total body fat, central obesity, and hyperinsulinemic insulin resistance. We examined the cross-sectional association between SHBG and impaired glucose tolerance (IGT) and NIDDM.

RESEARCH DESIGN AND METHODS — We conducted a cross-sectional study including 657 postmenopausal women, aged ≥50 years, who were not using hormone replacement therapy. Blood for SHBG and fasting plasma glucose was obtained concurrently in the morning; all women had a 75-g oral glucose tolerance test and measurement of BMI and waist-to-hip ratio (WHR).

RESULTS — SHBG was significantly associated with age, BMI, and WHR but not with smoking, physical activity, or alcohol intake. In these women, SHBG was significantly and independently inversely associated with IGT and with NIDDM.

CONCLUSIONS — These data strongly support an association between SHBG, or androgenicity, and diabetes in postmenopausal women. Because of the cross-sectional nature of this study, however, the directionality of the association is uncertain.

Sex hormone–binding globulin (SHBG), thought to be a marker for androgenicity (1), has been shown to be associated with obesity and visceral adiposity in postmenopausal women (2–5). Further, an association has been shown between BMI, an estimate of total body fat, waist-to-hip ratio (WHR), an estimate of abdominal adiposity, and several chronic diseases, including NIDDM (6,7). The link between SHBG and diabetes in postmenopausal women, however, has not been conclusive. Although some studies have reported an association between SHBG level and NIDDM (8,9), results in postmenopausal women have not been consistent (10).

The purpose of this study was to examine the independent cross-sectional association between SHBG level and impaired glucose tolerance (IGT) and NIDDM in a community-based sample of 657 elderly postmenopausal women, aged ≥50 years who were not using hormone replacement.

RESEARCH DESIGN AND METHODS

— Between 1984 and 1987, all surviving members of the Rancho Bernardo Heart and Chronic Disease Study, a middle to upper middle class community of older Caucasian adults in Southern California, were invited to a clinic visit; 80% of the women participated (11). A standardized questionnaire was completed that asked about demographic data, personal history of diabetes, cigarette smoking, alcohol consumption, physical activity, and use of selected medications. Medication use was validated by examination of prescriptions or pills brought to the clinic for that purpose. A 75-g oral glucose tolerance test was performed between 7:00 and 11:00 A.M. after a requested 12-h fast. Plasma glucose levels were measured by glucose oxidase assay before and 2 h after the glucose load. Fasting and 2-h serum insulin levels were determined by double-antibody radioimmunoassay (RIA) in the diabetes research laboratory of J.M. Olefsky (Department of Medicine, University of California, San Diego, CA), as previously described (12). Height and weight were measured with subjects in lightweight clothing without shoes; BMI was used to estimate obesity (calculated as [kg/m^2] × 100). Waist and hip girth were measured in centimeters over single-thickness clothing with the participant standing in an erect position with feet together. Waist was measured at the bending point (point marked when participant naturally bends forward and measured after participant has realigned to an upright position) and the narrowest circumference. Hip circumference was measured at the iliac crest and at the largest circumference. Waist and hip measures were highly correlated. Waist-to-hip ratio (WHR) was used to estimate upper body (central) obesity. To be consistent with our previously reported data, the bending point/iliac crest ratio was used as WHR for these analyses. Waist circumference (at the bending point) was used as an integrated measure of obesity and fat distribution, based on studies showing that waist circumference is highly correlated with both total and visceral body fat measured by computed tomography (CT) or magnetic resonance imaging (MRI) (13,14). Plasma for SHBG assays was frozen at −70°C.

A diagnosis of NIDDM and IGT was based on World Health Organization (WHO) criteria (15) as follows: *1*) NIDDM (fasting plasma glucose ≥140 mg/dl;

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IGT, impaired glucose tolerance; PCO, polycystic ovary disease; RIA, radioimmunoassay; SHBG, sex hormone–binding globulin; WHR, waist-to-hip ratio.

Table 1—*Baseline data by diabetes category for Rancho Bernardo women, 1984–1987*

	Normal	IGT	NIDDM
n	358	188	111
Age (years)	71.9 ± 8.4	75.9 ± 6.7*	74.5 ± 7.7*
BMI (kg/m²)	24.0 ± 3.5	25.0 ± 3.5*	25.7 ± 4.7*
Waist (centimeters)	77.6 ± 8.9	81.6 ± 9.8*	83.2 ± 11.3*
WHR	0.79 ± 0.06	0.82 ± 0.06*	0.83 ± 0.06*
Percent of current smokers	12.7	12.6	11.8
Percent of daily alcohol	38.5	36.8	27.3†
Percent exercise, 3 times/week	78.1	75.3	74.6

*$P < 0.01$, †$P < 0.05$ compared with normal.

and/or 2-h postchallenge glucose level ≥200 mg/dl; and/or history [diagnosed by a doctor]); 2) IGT (fasting plasma glucose <140 mg/dl; and 2-h plasma glucose 140–199 mg/dl). Reported diabetes was validated by review of medical records in a subset, with confirmation in over 85%.

Between 1992 and 1993, SHBG was measured in an endocrinology research laboratory by the method of Rosner (16), using first thawed specimens from the 1984–1987 venipuncture. The sensitivity and intra-assay and interassay coefficients of variation of SHBG were 0.10×10^{-8} mol/l and 7.5 and 8.0%, respectively.

The present study includes 657 women, aged ≥50 years, who were not using hormone replacement therapy. A total of 33 women with missing values, or who did not fast for 12 h, or who could not be classified were excluded. The single woman who reported insulin use was also excluded.

Data were analyzed using SAS and SAS/STAT (SAS Institute, Cary, NC). Because SHBG, 2-h glucose, and fasting and 2-h insulin levels showed a slightly skewed distribution, analyses were performed using log-transformed data. To aid in the interpretation of the results, mean values are presented for untransformed data; however, all *P* values are based on logged data. Student's *t* tests were used for continuous variables, and χ^2 tests were used for categorical variables to test for statistical significance by baseline mean values between categories of glucose tolerance. Mean age-adjusted SHBG levels were compared by categorical risk factor status. Pearson's partial correlation coefficients were used to compare the associations between log SHBG and fasting and 2-h glucose and insulin levels. Prevalence rates of IGT and NIDDM were calculated according to SHBG level below and above the median (1.73×10^{-8}), adjusting for age with the Mantel-Haenszel direct age adjustment, using a χ^2 test for statistical significance. Logistic regression models were used to assess the independent contribution of SHBG level to the prevalence of IGT and NIDDM in postmenopausal women, while adjusting for age, BMI, WHR, waist circumference, smoking, alcohol, and physical activity. All *P* values are two-tailed. Statistical significance was defined as $P < 0.05$.

RESULTS — Baseline data for these 657 women are shown in Table 1. Women with IGT or NIDDM were significantly older, more obese, and had greater central adiposity than normoglycemic women. Women with NIDDM were less likely to drink alcohol daily than nondiabetic women. Current cigarette smoking and physical activity did not differ by glucose tolerance status.

Age-adjusted mean SHBG levels dichotomized by BMI, WHR, waist circumference, cigarette smoking, alcohol use, and physical activity category are shown in Table 2. Although obese women and women with greater central obesity had significantly lower SHBG levels than lean women ($P < 0.0001$), SHBG levels did not differ significantly by current smoking, daily alcohol use, or regular exercise. Results were similar in women with normal glucose tolerance, IGT, or NIDDM (data not shown). Age-adjusted SHBG levels were highest for normoglycemic women (6.7×10^{-8}), lowest for women with NIDDM (4.7×10^{-8}), and intermediate for women with IGT (5.4×10^{-8}); all differences were statistically significant ($P < 0.001$). Adjustment for BMI or WHR did not materially alter these results. Similar results were found after stratification by oophorectomy status or use of diabetes medication (data not shown).

SHBG was significantly inversely correlated with 2-h glucose in women with NIDDM or normal glucose tolerance, with 2-h insulin in women with normal glucose

Table 2—*Age-adjusted mean SHBG ± SE by risk factor and glucose tolerance category for Rancho Bernardo women*

Risk factor	*n*	Mean ± SE	*P* value
BMI			
<27 kg/m²	498	6.4 ± 0.12	0.0001
≥27 kg/m²	159	4.5 ± 0.22	
WHR			
< 0.80	330	6.7 ± 0.16	0.0001
≥0.80	327	5.2 ± 0.15	
Waist circumference			
< 79 cm	329	6.9 ± 0.14	0.0001
≥79 cm	328	5.0 ± 0.15	
Current smoking			
No	577	5.9 ± 0.12	0.48
Yes	80	6.3 ± 0.32	
Physical activity (≥3 times/week)			
No	156	5.9 ± 0.12	0.48
Yes	501	6.0 ± 0.13	
Daily alcohol			
No	415	6.1 ± 0.14	0.49
Yes	242	5.8 ± 0.19	
Glucose tolerance			
Normal	358	6.7 ± 0.15	
IGT	188	5.4 ± 0.20	0.0001
NIDDM	111	4.7 ± 0.27	0.0001

Table 3—*Adjusted Pearson correlation coefficients (P value) of SHBG with fasting and 2-h insulin and fasting and 2-h plasma glucose by glucose tolerance status*

	Age-adjusted	Age-BMI–adjusted	Age-WHR–adjusted
Normal			
Fasting insulin	−0.11 (0.11)	−0.03 (0.64)	−0.09 (0.18)
Fasting plasma glucose	−0.10 (0.06)	−0.08 (0.15)	−0.10 (0.08)
2-h insulin	−0.18 (0.01)	−0.14 (0.05)	−0.15 (0.04)
2-h glucose	−0.15 (0.006)	−0.11 (0.04)	−0.16 (0.004)
Fasting insulin/fasting plasma glucose	−0.11 (0.12)	−0.05 (0.48)	−0.10 (0.16)
IGT			
Fasting insulin	−0.12 (0.86)	−0.02 (0.87)	−0.04 (0.65)
Fasting plasma glucose	−0.02 (0.81)	−0.03 (0.70)	−0.10 (0.08)
2-h insulin	−0.12 (0.19)	−0.13 (0.17)	−0.09 (0.35)
2-h glucose	0.01 (0.88)	0.007 (0.92)	0.006 (0.93)
Fasting insulin/fasting plasma glucose	0.03 (0.75)	0.006 (0.95)	0.07 (0.45)
NIDDM			
Fasting insulin	−0.20 (0.11)	−0.15 (0.25)	−0.20 (0.11)
Fasting plasma glucose	−0.26 (0.007)	−0.25 (0.01)	−0.25 (0.01)
2-h insulin	0.02 (0.86)	0.07 (0.59)	0.04 (0.78)
2-h glucose	−0.48 (0.0001)	−0.46 (0.0001)	−0.43 (0.0001)
Fasting insulin/fasting plasma glucose	−0.15 (0.24)	−0.10 (0.45)	−0.16(0.19)

tolerance, and with fasting plasma glucose in women with NIDDM (Table 3). Before adjusting for BMI, a borderline inverse association was seen between fasting plasma glucose and SHBG in women with normal glucose tolerance. No association was seen between SHBG and fasting insulin or the fasting insulin/fasting plasma glucose ratio in any category of glucose tolerance.

The percent of women who had normal glucose tolerance, IGT, or NIDDM according to the SHBG level above and below the median of 1.73×10^{-8} are shown in Table 4. Women with IGT or NIDDM were 3.4 times more likely to have an SHBG level below the median of 1.73×10^{-8}, and women with IGT were 2.1 times more likely to have an SHBG level below the median than the normoglycemic women ($P < 0.001$). As shown in Figure 1, within each glucose tolerance category, there was a significant linear increase (women with normal glucose tolerance) or decrease (women with IGT and NIDDM) in SHBG ($P < 0.001$).

In a multivariate analysis using logistic regression, with prevalent IGT or NIDDM as the dependent variable, low SHBG level, age, and WHR remained significant independent risk factors for IGT and NIDDM, and daily alcohol intake was also independently associated with NIDDM. BMI, exercise, and smoking were not independently associated with IGT or NIDDM after adjusting for WHR (Table 5). Substitution of WHR by waist circumference as an estimate of central adiposity did not materially alter these results.

CONCLUSIONS — In agreement with several other studies (2–5,9,17), this community-based cross-sectional study found a significant association between SHBG and three major NIDDM risk factors: age, body fat, and central obesity. In addition, we found a strong, independent, inverse association between SHBG level and IGT and NIDDM. This finding is consistent with a previous cross-sectional (8) and prospective (9) study that found lower mean SHBG levels in diabetic women compared with nondiabetic women, but inconsistent with a recent study by Haffner et al. (10), which found no significant association between SHBG and incident NIDDM in postmenopausal women. The latter study included only 19 postmenopausal women, which may explain its failure to find a SHBG-NIDDM association.

Other data support an association between hyperandrogenicity and insulin resistance, although the direction of the association is debated. Both anabolic steroids and oral contraceptives induce hyperinsulinemia and insulin resistance (18–20). Administration of insulin suppresses the production of SHBG in a human hepatic cell line (21). Women with polycystic ovary disease (PCO), a syndrome that may include hyperandrogenicity (22), typically have marked peripheral insulin resistance, glucose intolerance, and hyperinsulinemia, independent of obesity (23–25). Suppression of serum insulin levels by diazoxide in six obese women with PCO caused a significant increase in SHBG levels (26). Epidemiological studies suggest an SHBG-insulin association in postmenopausal women (27,28).

Low SHBG levels are associated with increased levels of bioavailable testosterone

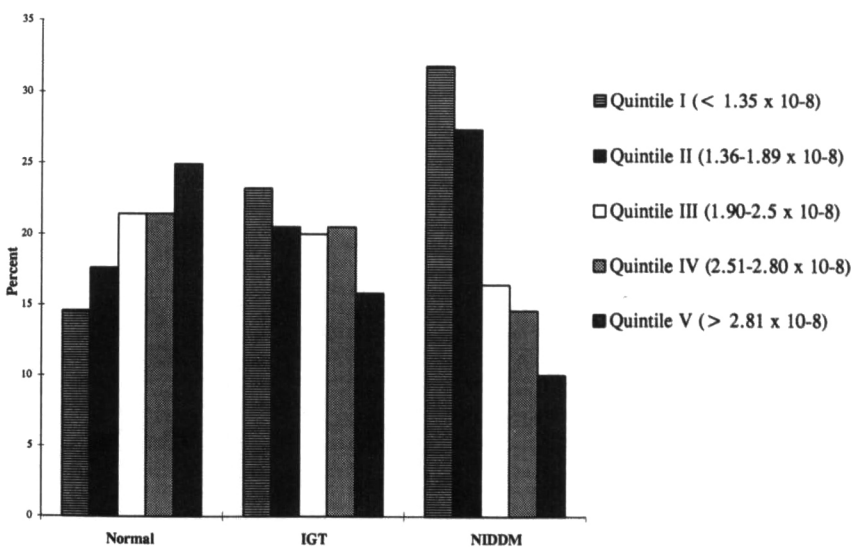

Figure 1—*Distribution of women by glucose status and quintile of SHBG.*

Table 4—*Proportion of women with NIDDM, IGT, and normoglycemia by SHBG level above or below median and age-adjusted prevalence ratio*

	SHBG level		
	$<1.73 \times 10^{-8}$	$\geq 1.73 \times 10^{-8}$	Age-adjusted prevalence ratio
NIDDM	24	16	3.43*
IGT	44	28	2.10*
Normal	32	56	

*$P < 0.001$ compared with normoglycemic women.

(7,29); therefore, an association between SHBG and NIDDM would also support an association between testosterone and NIDDM. Our findings are consistent with another study that found higher serum levels of testosterone in women with NIDDM (8).

WHR, a measure of visceral adiposity (30,31), has been shown to be associated with SHBG and total testosterone (2), insulin resistance (32,33), and NIDDM (6,7). The present study confirms an independent association between visceral adiposity and IGT and NIDDM in postmenopausal women, but found no independent association between total body fat and glucose tolerance status after adjusting for WHR. This is surprising because BMI was strongly correlated with body fat assessed by both dual-energy X ray absorptiometry and bioelectric impedance in this cohort (34). It is possible that an independent BMI-diabetes association was not seen because in this cohort, only 159 women were obese, defined as BMI ≥ 27 kg/m^2. These results are, however, concordant with a recent study of 25 premenopausal women, which found no significant association between total adipose tissue and insulin sensitivity after adjusting for abdominal adipose tissue (35).

To our knowledge, no study has directly measured the stability of frozen SHBG over time. Although one small study showed a negative correlation between the rate of SHBG-dihydrotestosterone dissociation and time >180 days (36), misclassification of SHBG would be expected to bias results toward the null, and the true SHBG-diabetes association could be stronger than reported here.

Because of the cross-sectional design of this study, it is not possible to determine whether decreased SHBG level is a cause or a consequence of NIDDM. Prospective studies evaluating the independent association between SHBG and androgens with NIDDM are necessary. If androgenicity precedes insulin resistance and diabetes, measurement of SHBG might help to identify individuals at risk of NIDDM. Understanding the mechanism for the SHBG-diabetes association could lead to intervention strategies to help prevent diabetes in postmenopausal women at risk.

Table 5—*Logistic regression models for association of glucose tolerance and SHBG level in Rancho Bernardo postmenopausal women*

	Normal vs. IGT			Normal vs. NIDDM		
	β	SE	*P* values	β	SE	*P* values
Model 1						
Age	0.09	0.01	0.00001	0.07	0.02	0.00001
SHBG	−0.17	0.03	0.00001	−0.31	0.05	0.00001
Model 2						
Age	0.09	0.01	0.00001	0.07	0.02	0.00001
SHBG	−0.15	0.04	0.0001	−0.28	0.05	0.00001
BMI	0.06	0.03	0.05	0.06	0.03	0.04
Model 3						
Age	0.08	0.02	0.00001	0.06	0.02	0.0009
SHBG	−0.14	0.04	0.0001	−0.27	0.05	0.00001
WHR	5.26	1.58	0.0009	6.57	1.94	0.0007
Model 4						
Age	0.08	0.02	0.00001	0.06	0.12	0.0006
SHBG	−0.13	0.04	0.0005	−0.26	0.05	0.00001
WHR	4.73	1.65	0.004	5.92	2.02	0.004
BMI	0.03	0.03	0.27	0.04	0.03	0.22
Model 5						
Age	0.08	0.12	0.00001	0.06	0.02	0.001
SHBG	−0.14	0.04	0.00001	−0.29	0.05	0.00001
WHR	5.13	1.59	0.001	6.36	1.96	0.001
Alcohol	0.02	0.10	0.84	0.31	0.13	0.02
Exercise	0.01	0.11	0.93	0.05	0.14	0.71
Smoking	−0.14	0.15	0.36	−0.20	0.19	0.29

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