Association of Decreased Sex Hormone Binding Globulin and Cardiovascular Risk Factors

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Sex hormones play a major role in determining the risk of cardiovascular disease. While earlier studies have shown that reduced sex hormone binding globulin (SHBG) is associated with increased glucose and insulin concentrations in premenopausal women, few data exist on the relationship of SHBG to other cardiovascular risk factors in women. We hypothesized that decreased SHBG would be associated with an atherogenic pattern of cardiovascular risk factors. We measured total testosterone, total estradiol and SHBG, lipids and lipoproteins, glucose and insulin, and systolic and diastolic blood pressure in 96 premenopausal women. Although total testosterone and total estradiol were not related to cardiovascular risk factors, SHBG was negatively associated with triglyceride concentration (r = -0.37) and positively associated with high density lipoprotein cholesterol (HDLc) (r = 0.42). After adjustment for overall adiposity (body mass index) and upper body adiposity (as measured by the ratio of waist-to-hip circumferences), SHBG was still positively related to HDLc, but not to triglyceride. Adjustment for insulin abolished the relationship between SHBG and triglyceride levels, but did not alter the relationship between SHBG and HDLc. Sex hormones were not related to either systolic or diastolic blood pressure. (Arteriosclerosis 9:136-143, January/February 1989)

Sex hormones play a major role in determining the risk of cardiovascular disease. Indirect evidence for this concept is provided by the higher triglyceride and low density lipoprotein cholesterol (LDLC) and lower high density lipoprotein cholesterol (HDLc) levels in men than in women. More direct evidence for the role of sex hormones as determinants of cardiovascular risk factors is provided by studies showing that exogenous androgen administration increases LDLc and decreases HDLC. Conversely, administration of estrogen to postmenopausal women with familial hypercholesterolemia is associated with decreased LDLc and increased HDLC.

Sex hormone binding globulin (SHBG) may also be an important predictor of lipids and lipoproteins, since it is the major determinant of the ratio of free to bound plasma testosterone and other androgens. Although decreased SHBG and increased percent free testosterone have been associated with increased glycemia and insulinemia in premenopausal women, few data exist on the relationship of endogenous sex hormones and SHBG to lipids and lipoproteins. Studies to date suggest that SHBG is positively associated with HDLC in both premenopausal and postmenopausal women.

The relationship between SHBG, sex hormones, and cardiovascular risk factors could be confounded by obesity and body fat distribution. Both overall adiposity and upper body adiposity are associated with increased triglyceride and decreased HDLC, as well as with decreased SHBG. Thus, the increased atherogenic pattern of lipids and lipoproteins observed with decreased SHBG could be due to differences in obesity, body fat distribution, or both. Increased hypertension, systolic blood pressure, or both have also been observed with increased overall adiposity and upper body adiposity. Few data exist, however, on the relationship of blood pressure to alterations in sex hormones.

In this report, we will examine the relationship of sex hormones and SHBG to cardiovascular risk factors in 96 premenopausal women. We will also examine whether associations between cardiovascular risk factors, sex hormones, and SHBG are due to the confounding effects of obesity and body fat distribution.

Methods

Population

The San Antonio Heart Study is a population-based study of cardiovascular risk factors and diabetes in Mexican Americans and non-Hispanic whites. Full descriptions of the study design and response rates have been published previously. The present report concerns a subsample of the overall San Antonio Heart Study population; all premenopausal women residing in a middle-income neighborhood were identified. Subjects were considered to be premenopausal if their last menstrual period was less than 60 days before their clinic visit and if they had had at least 10 menstrual periods in the preceding year. Subjects who reported having had a hysterectomy

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or ovariectomy or who reported taking oral contraceptives or estrogens were excluded from the present analyses. Of the 113 women who met these criteria, frozen serum contingency samples were available on 96 individuals whose ages were 25 to 54 years. These specimens were analyzed for SHBG and sex hormone concentrations. Ethnic classification (Mexican American and non-Hispanic white) was based on a previously published algorithm.24

**Procedures**

Anthropometric measurements (height, weight, and waist and hip circumferences) were made with the participant wearing an examination gown after having removed her shoes and upper garments. Waist circumference was measured at the level of the umbilicus and hip circumference at the level of the greater trochanter. The average of two readings was taken as the measurement of each circumference. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. The ratio of waist-to-hip circumference (WHR) was chosen as the measure of upper body adiposity.

Systolic (first phase) and diastolic (fifth phase) blood pressures were measured to the nearest even digit using a random-zero sphygmomanometer (Hawksley-Gelman, London, England) on the right arm of the seated participant following at least a 5-minute rest. Three readings were recorded for each individual, and the average of the second and third reading was defined as the patient's blood pressure.25 Individuals who met the Hypertension Detection and Follow-up Program definition of hypertension (diastolic blood pressure ≥95 mm Hg or currently taking antihypertensive medications25) were excluded from this report.

Blood samples obtained after a 12-hour fast were tested for serum total and HDL cholesterol, triglyceride, and insulin concentrations and for plasma glucose concentration. After the fasting blood sample was obtained, a 75 g glucose-equivalent load (Koldex or Orangedex, Custom Laboratories, Baltimore, MD) was administered, and blood samples were obtained 0.5, 1, and 2 hours later for plasma glucose and serum insulin determinations. The sum of these values plus the fasting value (referred to as glucose and insulin sum, respectively) were used as overall measures of glycemia and insulinemia. Glucose concentrations were measured using an Abbott Biochromatic Analyzer (Abbott Laboratories, South Pasadena, CA). Serum insulin concentrations were measured with a commercial solid-phase radioimmunoassay kit (Diagnostic Products Corporation, Los Angeles, CA). Subjects with diabetes according to the National Diabetes Data Group criteria26 were excluded from the present report.

**Lipoprotein and Sex Hormone Measurements**

Lipid and lipoprotein methods have been described previously.12,27 Total HDL cholesterol was measured in the supernatant after precipitation with dextran sulfate-MgCl$_2$.27 A second precipitation, performed using double the concentration of dextran sulfate, yielded HDL$_2$ cholesterol in the supernatant.28 After correction for dilution, the HDL$_2$ cholesterol was calculated as the difference between total HDL cholesterol and HDL$_3$ cholesterol. In other studies, the HDL$_2$ cholesterol values measured by the two-stage dextran sulfate-MgCl$_2$ method have been found to be highly correlated with those measured by the heparin-MnCl$_2$-dextran sulfate method28 or by analytical ultracentrifugation (r=0.95).29,30 Only five subjects had cholesterol levels higher than 420 mg/dl, and one subject had triglyceride levels higher than 280 mg/dl. Since inclusion of these subjects did not alter the results of the report, these subjects were not excluded.

Contingency serum samples from the fasting, 0.5-, 1-, and 2-hour samples were frozen at −70°C within 48 hours and were not thawed until the analyses for sex hormones were performed (an average of 15 months later). After thawing, all four timed specimens for a given individual were pooled. SHBG was measured by the dextran-coated charcoal method.30 Total testosterone was measured by a coated tube commercial radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA), and total estradiol was measured by a commercial double antibody radioimmunoassay (Panetix, Santa Monica, CA). Percent free testosterone was calculated from the SHBG and total testosterone concentrations by using a computer program that calculates the equilibrium distribution of steroid hormones according to the law of mass action.31

**Statistical Analyses**

The following BMDP statistical packages32 were used: Spearman correlation coefficients (3S); multiple linear regression (2R); age-adjusted means by analyses of covariance (1V and 2V). The BMDP-P2V program computes first order interactions (e.g., WHR X BMI). None of the first order interactions were statistically significant. Triglyceride concentrations were log-transformed to improve skewness and kurtosis.

The analyses presented in Tables 1 and 2 and Figures 2 and 3 were initially performed separately for each ethnic group. Since the relationships between sex hormones and metabolic variables were similar in each ethnic group, the two ethnic groups were pooled to simplify the presentation. For example, the correlation between SHBG and HDL cholesterol was 0.41 in Mexican Americans and 0.45 in non-Hispanic whites (Figure 1A). Since estradiol and testosterone levels vary during the menstrual cycle and concentrations of HDL cholesterol are higher in the follicular stage of the menstrual cycle,33 statistical analyses were also performed on a subgroup of women (n=42) who, based on the date of their last menstrual period, were considered to be in the early follicular stage. Since the relationships between sex hormones and metabolic parameters for this subgroup were similar to those for the entire group (n=96), only the latter are reported.

**Results**

Table 1 presents summary statistics for the anthropometric variables, sex hormones, and cardiovascular risk factors. The age range was 25 to 54 years. The mean age was 35.0±0.9 years.

Table 2 shows Spearman correlation coefficients between the sex hormones, anthropometric variables, and cardiovascular risk factors. HDL, HDL$_2$, and HDL$_3$...
cholesterols were negatively correlated with BMI and WHR, whereas triglyceride concentration and systolic and diastolic blood pressure were positively correlated with these anthropometric variables. WHR was a better predictor than BMI of lipids and lipoproteins, although not of systolic or diastolic blood pressure. Total cholesterol and LDL cholesterol were not correlated with anthropometric variables. HDLC, HDL₂C, and HDL₃C were positively correlated with SHBG and negatively correlated with percent free testosterone; the reverse pattern was observed for triglyceride concentration. Since total cholesterol, LDL cholesterol, and systolic and diastolic blood
Table 2. Spearman Correlation Coefficients between Sex Hormones, Anthropometric Variables, and Cardiovascular Risk Factors

| Variable                        | Cholesterol | Blood pressure |
|---------------------------------|-------------|----------------|
|                                 | HDL | HDL₂ | HDL₃ | Total | LDL | Triglyceride | Diastolic | Systolic |
| Body mass index (kg/m²)         | −0.320‡| −0.340‡| −0.157| 0.083| 0.112| 0.360‡| 0.251*| 0.226* |
| WHR                             | −0.415‡| −0.445‡| −0.230*| 0.116| 0.125| 0.390‡| 0.221*| 0.170  |
| SHBG                            | 0.420‡| 0.435‡| 0.256‡| 0.128| 0.128| −0.368‡| 0.125| 0.138  |
| Total testosterone              | 0.052| −0.002| 0.089| 0.126| 0.126| 0.035| 0.095| 0.110  |
| % Free testosterone             | −0.382‡| −0.405‡| −0.273†| −0.128| −0.140| 0.280†| −0.041| 0.044  |
| Total estradiol                 | 0.148| 0.158| −0.079| 0.040| 0.038| −0.073| −0.027| 0.054  |

HDL = high density lipoprotein, LDL = low density lipoprotein, WHR = waist-to-hip ratio, and SHBG = sex hormone binding globulin.

*p < 0.05, †p < 0.01, ‡p < 0.001.

pressures were not significantly correlated with sex hormones or SHBG, they will not be discussed further in this report. Scatter plots for the relationship between SHBG and HDLc and triglyceride are shown in Figure 1. SHBG was negatively correlated with BMI (r = −0.46, p < 0.001) and WHR (r = −0.30, p < 0.01).

Since HDLc, HDLc₂, HDLc₃, and triglyceride are correlated with BMI and body fat distribution, 12,13 and since decreased SHBG is also associated with these variables, 7,17 we also examined the association of these metabolic variables with SHBG after controlling for BMI and WHR. SHBG remained significantly positively correlated with HDLc (partial correlation coefficient r = 0.227, p < 0.05) and HDLc₂ (r = 0.291, p < 0.01), but not with HDLc₃ (r = 0.173) or triglyceride levels (r = 0.143). Compared to the correlations presented in Table 2, these associations were moderately attenuated after adjusting for the anthropometric variables. The partial correlations of percent free testosterone with these metabolic variables, after adjusting for anthropometric variables, were similar to those with SHBG, but opposite in sign (data not shown). This is expected since the correlation between SHBG and percent free testosterone was −0.95. SHBG, however, was not significantly related to either total testosterone (r = −0.220) or total estradiol (r = −0.031).

Figures 2 and 3 show the relationships between triglyceride and HDL cholesterol (as dependent variables) and BMI, WHR, and SHBG (as independent variables). As shown in Figure 2A, triglyceride was independently related to both SHBG (r = 0.045) and BMI (r < 0.001). Figure 2B shows that triglyceride was negatively related to SHBG (r = 0.031) and positively related to WHR (r = 0.002). Figure 3 shows the relationship between HDL cholesterol and SHBG, BMI, and WHR. HDL cholesterol was positively related to SHBG (r = 0.010), but not to BMI (r = 0.033, Figure 3A). HDL cholesterol was significantly related to both SHBG and WHR (r < 0.01, Figure 3B).

Previous data have suggested that SHBG is inversely associated with hyperglycemia and hyperinsulinemia (r = −0.27, p < 0.01 and r = −0.54, p < 0.001, respectively) both in our population and in others. 8 Since impairment of glucose tolerance and noninsulin-dependent diabetes mellitus are also associated with decreased HDLC and increased triglyceride concentrations, 34,35,36 we considered whether the association between decreased SHBG and lipoprotein abnormalities in Table 2 and Figures 2 and 3 might be a consequence of hyperinsulinemia. After controlling for insulin sum, SHBG was still significantly positively associated with HDLC (partial correlation coefficient r = 0.296, p < 0.01), but no longer significantly associated with triglyceride concentrations (r = −0.143). Conversely, after controlling for SHBG, insulin sum was still significantly positively correlated with triglyceride levels (r = 0.275, p < 0.1), but not significantly correlated with HDLC (r = −0.160). Thus, the relationship between SHBG
and HDL was statistically independent of obesity, body fat distribution, and insulinemia, but the relationship between SHBG and triglyceride concentrations was dependent on insulinemia.

Table 3 shows the results of multiple linear regression analyses with serum triglyceride as the dependent variable. Independent variables are shown in the order they entered the regression model. In model 1, WHR, age, SHBG, and BMI are the independent variables. Both WHR and age were significantly positively associated, and SHBG, significantly negatively associated with triglyceride levels. In model 2, glucose sum and insulin sum were included in addition to the independent variables listed in model 1. Insulin sum, age, and WHR were strongly positively related to triglyceride levels. After the addition of insulin and glucose sum, SHBG was no longer significantly associated with triglyceride levels.

Table 4 shows the results of multiple linear regression analyses with HDL cholesterol as the dependent variable. In model 1, SHBG was strongly positively associated and WHR was strongly negatively associated with HDLC. Age and BMI were not significantly related to HDLC. In model 2, neither insulin sum nor glucose sum entered the regression model. Since HDL is inversely related to triglyceride concentration, we also added triglyceride to model 2. SHBG was still significantly related to HDL cholesterol after the addition of triglyceride to model 2 ($p<0.01$). The regression coefficient for SHBG was slightly reduced to 1.1 (from 1.1 in Table 4).

To reduce the confounding effects of obesity and body fat distribution on the relationship between SHBG and metabolic variables, we constructed subgroups of individuals, who were closely matched on age, BMI, and WHR, but with either high or low SHBG concentrations. The
results of analyses performed on these subgroups are shown in Table 5. HDL and HDL₂ cholesterol were significantly lower in the low SHBG subgroup, whereas insulin sum was significantly higher in this subgroup. No other variable was significantly different (p>0.10) in the low vs. high SHBG subgroups, although in view of the small numbers of subjects, one must be cautious about the possibility of a type II error.

Discussion

The present results indicate that decreased levels of SHBG in premenopausal women are associated with increased levels of triglyceride and decreased levels of HDL and HDL₂ cholesterol. The relation of SHBG with HDL cholesterol appears to be independent of both obesity and body fat distribution. However, the relationship of SHBG with triglyceride concentrations appears to be partially dependent on obesity and body fat distribution possibly through the effect of obesity and body fat distribution on hyperinsulinemia. SHBG was, in general, not significantly related to total or HDL cholesterol or to triglyceride or diastolic blood pressure. Total testosterone and total estradiol were not associated with lipid or lipoprotein levels. Percent free testosterone (derived from SHBG and total testosterone) was negatively associated with HDL and HDL₂ cholesterol and positively correlated with triglyceride levels. (This is not surprising since percent free testosterone is highly negatively correlated with SHBG.) Previous studies have suggested that SHBG is positively related to HDL in both premenopausal and postmenopausal women. These latter studies, however, did not report on HDL fractions, nor did they take account of the effect of body fat distribution.

The literature on sex hormones in men is extensive and somewhat inconsistent. Two recent reports have suggested a positive association between HDL cholesterol and SHBG and also a positive association between estradiol and LDL cholesterol. In one of these studies, total testosterone was negatively associated with HDL and HDL₂ cholesterol. In contrast, several other studies have reported positive associations between HDL and total testosterone. Stefanik et al. have suggested that these discrepancies may be due to the confounding effects of other variables, for example, cigarette smoking, alcohol consumption, and upper body adiposity. It is of interest that Semmens et al. found a negative relationship between HDLC and total testosterone in a group of Mormons and Seventh Day Adventists who usually have low levels of alcohol and cigarette consumption. The women in our population also tended to drink relatively low amounts of alcohol and smoke relatively few cigarettes. (We also included smoking, alcohol, and exercise in regression analyses analogous to those shown in Table 4, but the addition of these covariates did not substantially alter the results shown in the table). Thus, differences in lifestyles may explain some of the reported gender differences in associations of lipids and sex hormones.

The physiologic mechanisms that underlie the association between decreased SHBG and metabolic variables remain unclear. In the present study, we found that SHBG, but not total testosterone or estradiol, were related to metabolic variables. This is consistent with the concept that binding of sex hormones to plasma proteins, including SHBG, determine tissue uptake and subsequent activity of sex hormones in vivo. Since SHBG is the most important determinant of the plasma distribution of testosterone in normal men and women, SHBG may be a sensitive in vivo indicator of both free and SHBG-bound androgen levels. Recently, SHBG has been shown to affect the cellular availability of testosterone in men. Thus, SHBG may reflect intracellular availability of testosterone better than total hormone concentrations. Moreover, decreases

| Table 5. Cardiovascular Risk Factors in Subgroups with High and Low SHBG Concentrations |
|-----------------------------------------------|----------|----------|----------|
| Risk factor | Low SHBG | High SHBG | P        |
| N          | 24       | 24       |          |
| Age (yrs)  | 33.7     | 34.4     | NS       |
| BMI (kg/m²)| 28.3     | 26.2     | NS       |
| WHR        | 0.78     | 0.76     | NS       |
| SHBG (µg/dl)| 0.99     | 0.556    | p<0.001  |
| HDL cholesterol (mg/dl) | 44.8 | 51.2 | p<0.01 |
| HDL₂ cholesterol (mg/dl) | 11.70 | 16.0 | p<0.01 |
| HDL₃ cholesterol (mg/dl) | 34.7 | 35.0 | NS       |
| LDL cholesterol (mg/dl) | 109.1 | 114.5 | NS       |
| Total cholesterol (mg/dl) | 176.2 | 183.4 | NS       |
| Triglyceride (mg/dl) | 100.1 | 92.3 | NS       |
| Systolic BP (mm Hg) | 114.7 | 117.9 | NS       |
| Diastolic BP (mm Hg) | 70.2 | 74.0 | NS       |
| Glucose sum (mg/dl) | 480 | 465 | NS       |
| Insulin sum (µU/ml) | 412.6 | 260.4 | p<0.01 |

The total population (n=98) was divided into two groups based on the median SHBG value: low SHBG≤0.29 µg/dl and high SHBG≥0.29 µg/dl. 24 pairs of subjects who met the following matching criteria were chosen:

- WHR=waist-to-hip ratio
- SHBG=sex hormone binding globulin
- BMI=body mass index
- HDL=high density lipoprotein
- LDL=low density lipoprotein
- BP=blood pressure.

The matching criteria were: Age≥2 years, BMI≥2 kg/m², and WHR≥0.02.
in SHBG are associated with a greater rise in free testosterone than in free estradiol because the affinity of SHBG for testosterone is greater than for estradiol. Thus, despite a rise in free estradiol with decreased SHBG, reduced binding globulin may shift the relative androgen-to-estrogen balance toward increased androgenicity.6

Because the present study was cross-sectional, no direct inference can be made about causality or temporal relationships between body fat distribution, lipids and lipoproteins, and sex hormones. Administration of exogenous androgens can cause hypertriglyceridemia, hyperglycemia, and hyperinsulinemia.53-54,55 Increased percent free testosterone and total testosterone are associated with insulin resistance independence of obesity in premenopausal women.54 On the other hand, hyperinsulinemia can cause increased androgen production by the ovary,56 and insulin has recently been shown to suppress the production of SHBG in a human hepatoma cell line.57 In this report, we have proposed that increased androgenicity (as measured by decreased SHBG) is associated with increased insulin and triglyceride concentrations and decreased HDL cholesterol, but we cannot exclude the possibility that the decreased SHBG and HDL cholesterol are both consequences of hyperinsulinemia. Multivariate analyses such as those presented in this study can identify statistical predictors of metabolic abnormalities but do not necessarily imply that the variable or variables that drop out of the multivariate model are unimportant in the pathophysiology of the particular metabolic effect examined.

It is of interest that overall adiposity (BMI) and upper body adiposity (WHR) were strongly associated with increased triglyceride and decreased HDL cholesterol in simple correlation analyses (Table 2). As in previous reports,12,13,29 WHR was more strongly correlated with lipids and lipoproteins than was BMI (Tables 2 to 4). Moreover, adjustment for SHBG (Figures 2 and 3 and Tables 3 and 4) did not abolish the association between WHR and these lipid variables. The addition of insulin sum, on the other hand, did attenuate the effect of WHR on triglyceride concentration, although not on HDL concentration. These findings suggest that the effect of obesity and body fat distribution on triglyceride may be mediated in large part through hyperinsulinemia.

Estrogen has been reported to increase apolipoprotein A-I synthesis in premenopausal women.60 Anabolic steroid administration may decrease HDL cholesterol by more than 50% without changing triglyceride levels.3,49 Hepatic triglyceride lipase may provide a mechanism whereby changes in HDL-C occur without changes in triglyceride. Tikkkanen et al.50 have proposed that the influence of sex steroids on HDL-C concentrations is mainly mediated through hepatic triglyceride lipase. Hepatic triglyceride lipase is negatively correlated with HDL cholesterol, but shows little association with VLDL cholesterol.51 Hepatic triglyceride lipase is also increased by anabolic steroids,3,51 is lower in women than in men,51,52 and is decreased by ethinyl estradiol.51 Since both Evans et al.53 and our group54 have shown that premenopausal women with upper body adiposity have increased percent free testosterone and decreased sex hormone binding globulin, it is possible that the effect of body fat distribution on HDL cholesterol may be mediated through alterations in hepatic triglyceride lipase. However, no study thus far has directly examined the effect of body fat distribution on hepatic triglyceride lipase.

In summary, we have shown in a group of 96 premenopausal women that upper body adiposity and decreased SHBG are associated with alterations in lipids and lipoproteins. Multivariate analyses suggest that increased androgenicity may mediate the association of BMI with low HDL cholesterol; these changes may, in turn, be mediated by elevations in hepatic triglyceride lipase. The effect of upper body adiposity on triglyceride concentration, in contrast, might be mediated through impairment of glucose tolerance and hyperinsulinemia. Further work in metabolic ward settings will be needed to confirm these hypotheses.

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