Sex Hormone–Binding Globulin Levels in Middle-Aged Premenopausal Women

Associations with visceral obesity and metabolic profile

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OBJECTIVE — Low sex hormone–binding globulin (SHBG) levels in women are associated not only with hyperinsulinemia, increased risk for cardiovascular disease, and type 2 diabetes but also with excess body fatness and abdominal obesity. We tested the hypothesis that an elevated total or intra-abdominal adipose tissue accumulation mediates the relationship between low SHBG levels and an altered metabolic profile.

RESEARCH DESIGN AND METHODS — We measured body composition (dual-energy X-ray absorptiometry [DEXA]) and body fat distribution (computed tomography) in 52 middle-aged (46.7 ± 0.4, mean ± SEM) premenopausal women. Insulin and glucose responses to a 75-g oral glucose load and plasma lipid-lipoprotein levels were also measured.

RESULTS — Low plasma SHBG concentrations were associated with increased total body fat mass ($r = -0.41$, $P < 0.005$) and subcutaneous abdominal ($r = -0.39$, $P < 0.005$) and intra-abdominal ($r = -0.37$, $P < 0.008$) adipose tissue area. Low SHBG was also associated with a greater insulin response to oral glucose ($r = -0.40$, $P < 0.005$), higher triglyceride levels ($r = -0.29$, $P < 0.05$), higher cholesterol/HDL cholesterol ratio ($r = -0.51$, $P < 0.005$), but lower HDL cholesterol concentrations ($r = 0.65$, $P < 0.005$). When matched for intra-abdominal fat or total fat mass, subjects with either low or high SHBG showed no difference in the insulin response to an oral glucose challenge. Statistical adjustment for differences in intra-abdominal adipose tissue accumulation or total body fat mass also eliminated the associations between SHBG levels and metabolic variables, with the exception of the association between SHBG and HDL cholesterol levels ($r = 0.52$, $P < 0.005$).

CONCLUSIONS — Our results suggest that the previously reported relationship between low SHBG levels and increased metabolic disease risk in women is mediated, to a large extent, by concomitant variation in body fatness and intra-abdominal adipose tissue accumulation.

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In women, increased androgenicity, as reflected by low circulating SHBG concentrations, has been related to hyperinsulinemia, glucose intolerance, and insulin resistance, as well as to the risk of cardiovascular disease and type 2 diabetes (1–7). Reduced SHBG level has also been associated with an adverse blood lipid profile, including reduced HDL cholesterol concentrations (1,8,9). Its role as an independent marker of cardiovascular disease risk, however, is uncertain (10).

An androgenic sex steroid profile as reflected by low circulating SHBG is also associated with an increased accumulation of abdominal fat in women (11–13). Because obesity and excess intra-abdominal adipose tissue have been associated with an altered metabolic profile (14,15), it is unclear whether the association between SHBG levels and an adverse metabolic profile is mediated by differences in total or intra-abdominal adipose tissue accumulation. Most studies that have addressed this question have used surrogates of adiposity measures, such as BMI and waist-to-hip ratio (WHR). Control for these variables attenuated the relationship between SHBG and metabolic variables in some studies (7,9,16), although results are divergent (8). To our knowledge, no study has examined the relationship between SHBG and an altered metabolic profile after controlling for direct measures for both total and intra-abdominal adiposity.

To address this issue, we measured SHBG, body fatness (dual-energy X-ray absorptiometry [DEXA]), fat distribution (computed tomography), glucose/insulin homeostasis indices, and cardiovascular disease risk factors in a sample of 52 middle-aged premenopausal women. We tested the hypothesis that elevated intra-abdominal adipose tissue accumulation and body fatness would explain a major part of the relationship between low SHBG levels and an altered metabolic profile.

RESEARCH DESIGN AND METHODS

Study subjects

Volunteers in the present study were recruited to participate in the Vermont Longitudinal Study of the Menopause, a 5-year study examining changes in energy expenditure, body composition, and metabolic profile associated with the natural menopause transition. A total of 52 healthy, middle-aged (46.7 ± 0.4 years) premenopausal women were studied. They were recruited from Burlington, VT, and surrounding areas through advertisement in local newspapers. To be included in the study, women had to be nonsmokers and of stable weight (within ±2 kg, 6 months before testing). They also had to have a nor-

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Abbreviations: AUC, area under the curve; DEXA, dual-energy X-ray absorptiometry; OGTT, oral glucose tolerance test; 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.

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Table 1—*Physical characteristics of the 52-women sample*

	Mean ± SEM	Range
Age (years)	46.7 ± 0.4	40.0–52.0
Body weight (kg)	63.9 ± 1.4	47.0–104.0
BMI (kg/m^2)	23.3 ± 0.5	18.3–32.8
Fat mass (kg)	19.1 ± 1.2	8.0–45.3
Fat-free mass (kg)	41.0 ± 0.6	34.0–54.3
Abdominal adipose tissue areas (cm^2)		
Subcutaneous	243.5 ± 16.2	32.2–572.7
Intra-abdominal	65.7 ± 5.4	23.9–185.0
Fasting insulin (pmol/l)	49.0 ± 2.3	35.9–96.9
Fasting glucose (mmol/l)	4.6 ± 0.1	3.4–5.8
Cholesterol (mmol/l)	4.60 ± 0.13	3.1–7.6
Triglycerides (mmol/l)	1.00 ± 0.08	0.42–3.54
HDL cholesterol (mmol/l)	1.47 ± 0.05	0.88–2.35
LDL cholesterol (mmol/l)	2.92 ± 0.12	1.69–5.92
Cholesterol/HDL cholesterol (mmol/l)	3.27 ± 0.14	1.88–6.92
SHBG (nmol/l)	53.2 ± 3.41	15.0–115.0
Testosterone (ng/ml)	0.27 ± 0.01	0.09–0.51
Free androgen index	0.65 ± 0.06	0.12–2.56

mal electrocardiogram at rest and during an exercise test. Middle-aged premenopausal women were recruited according to age criteria (between 40 and 52 years) and premenopausal status, as defined by having two menses in the 3 months preceding testing, no increase in cycle irregularity in the 12 months preceding testing, and a follicle-stimulating hormone level <30 IU/l. Exclusion criteria were pregnancy; history or diagnosis of diabetes, heart disease, hypertension, or other chronic diseases; hormone replacement therapy; chronic steroid therapy; a history of alcohol or drug abuse; and glucose intolerance, defined as a 2-h glucose level of >140 mg/dl after a 75-g oral glucose load. The experimental protocol was approved by the Committee on Human Research at the University of Vermont, and each subject gave written consent to participate in the study.

Experimental protocol

Each volunteer underwent an outpatient screening visit and was instructed on how to record her menstrual cycle. A medical history, a physical examination, biochemical laboratory tests, a 75-g oral glucose tolerance test (OGTT), and an exercise stress test were performed during the outpatient screening visit. Approximately 2 months after the screening visit, subjects were admitted to the General Clinical Research Center for an overnight visit. The overnight visit occurred during the follicular phase of the menstrual cycle in 39 patients and during the luteal phase in 13 patients. Fasting blood draws, body composition, and adipose tissue distribution measures were performed during this visit.

Body composition and adipose tissue distribution

Fat mass and fat-free mass were measured by DEXA using a Lunar DPX-L densitometer (Lunar, Madison, WI) as previously described (17). All scans were analyzed using the Lunar Version 1.3 DPX-L extended-analysis program for body composition. Test-retest coefficient of variation for this measurement was 1.2% for fat mass and 2% for fat-free mass.

Intra-abdominal and abdominal subcutaneous adipose tissue areas were measured by computed tomography with a GE High Speed Advantage CT scanner (General Electric Medical Systems, Milwaukee, WI) as previously described (18). Subjects were examined in the supine position with both arms stretched above the head. The scan was performed at the L4-L5 vertebrae level using a scout image of the body to establish the precise scanning position. Intra-abdominal adipose tissue area was quantified by delineating the intra-abdominal cavity at the most internal aspect of the abdominal and oblique muscle walls surrounding the cavity and the posterior aspect of the vertebral body with the computer interface of the scanner. Adipose tissue was highlighted and computed using an attenuation range from −190 to −30 Hounsfield Units. The subcutaneous adipose tissue area was quantified by highlighting adipose tissue located between the skin and the most external aspect of the abdominal muscle wall.

Plasma SHBG and testosterone levels

Plasma testosterone and SHBG concentrations were determined by radioimmunoassay (Diagnostic, Webster, TX). Coefficients of variation for the testosterone assay were 7.7% for intra-assay and 10.5% for interassay. Coefficients of variation for SHBG were 2.7% for intra-assay and 4.0% for interassay. The free androgen index was calculated as the ratio testosterone/SHBG × 100.

OGTT

A 75-g OGTT was performed after an overnight fast (~0800). Blood samples were collected at 0, 60, 90, and 120 min for analysis of glucose and insulin levels. Glucose was measured by the glucose oxidase method using an automated analyzer (YSI, Yellow Springs, OH). Serum insulin was determined with a double antibody radioimmunoassay (Diagnostic, Los Angeles, CA). Intra-assay and interassay coefficients of variation were 4 and 10%, respectively. Glucose and insulin total areas under the curve (AUC) were determined using the trapezoid method.

Plasma lipids and lipoprotein levels

Enzymatic processes were used to determine plasma triglyceride levels (19) and total and HDL cholesterol concentrations (20). Cholesterol concentrations in the HDL fraction were determined after precipitation with dextran sulfate of lipoproteins containing apolipoprotein B (21). LDL cholesterol concentrations were calculated using the Friedewald equation (22).

Statistical analyses

Data are presented as means ± SEM. Because no differences in outcome variables were found between women tested in the luteal versus the follicular phase, data were pooled for analyses. Pearson's correlation coefficients were computed to evaluate the magnitude of the associations between SHBG and metabolic variables. For correlational analyses, the following variables were $\log_{10}$ transformed: fasting insulin, insulin AUC during the OGTT, insulin/glucose AUC ratio, cholesterol, LDL cholesterol,

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triglycerides, and cholesterol/HDL cholesterol ratio. To control for the influence of intra-abdominal fat on metabolic variables, individuals with either high or low SHBG levels were matched for intra-abdominal fat (average difference = 3.1 ± 4.1 cm^2). We also matched individuals with either low or high intra-abdominal fat for SHBG (average difference = 0.9 ± 1.2 nmol/l) to examine the effects of elevated intra-abdominal fat on outcome variables, independent of SHBG. Comparisons of matched subgroups were performed by Student's *t* test. Partial correlation analysis was used to evaluate the magnitude of the associations between SHBG and variables of the metabolic profile after adjustment for adiposity measures based on a linear model.

RESULTS — Physical characteristics of the women of the study are shown in Table 1. As expected from the inclusion criteria, women of the study had a healthy metabolic profile. Although there was wide variation in physical characteristics, subjects were characterized by relatively low abdominal subcutaneous and intra-abdominal adipose tissue accumulations and a desirable lipid profile according to clinical recommendations (23), with a mean cholesterol level <5.2 mmol/l and HDL cholesterol >0.91 mmol/l.

Associations between SHBG levels and adiposity measures are shown in Fig. 1. A lower SHBG level was associated with a higher total body fat mass ($r = -0.41$, $P < 0.005$) and subcutaneous ($r = -0.39$, $P < 0.005$) and visceral ($r = -0.37$, $P < 0.008$) adipose tissue areas. As shown in Fig. 1, linear and logarithmic models were used to fit the relationships between adiposity and SHBG. The variance explained by the two models was not different for all three measures of adiposity (not shown). The relationship between SHBG and intra-abdominal adipose tissue area was also modeled by a quadratic function that generated a significant quadratic term (not shown).

Table 2 shows the Pearson's correlation coefficients between SHBG levels and metabolic variables. Low plasma SHBG level was associated with increased fasting insulin ($r = -0.27$, $P = 0.05$), an increased insulin response to the glucose load ($r = -0.40$, $P < 0.005$), and an altered lipid-lipoprotein profile, including reduced HDL cholesterol ($r = -0.65$, $P < 0.005$), increased triglyceride levels ($r = -0.29$, $P < 0.05$), and an increased cholesterol/HDL cholesterol ratio ($r = -0.51$, $P < 0.005$).

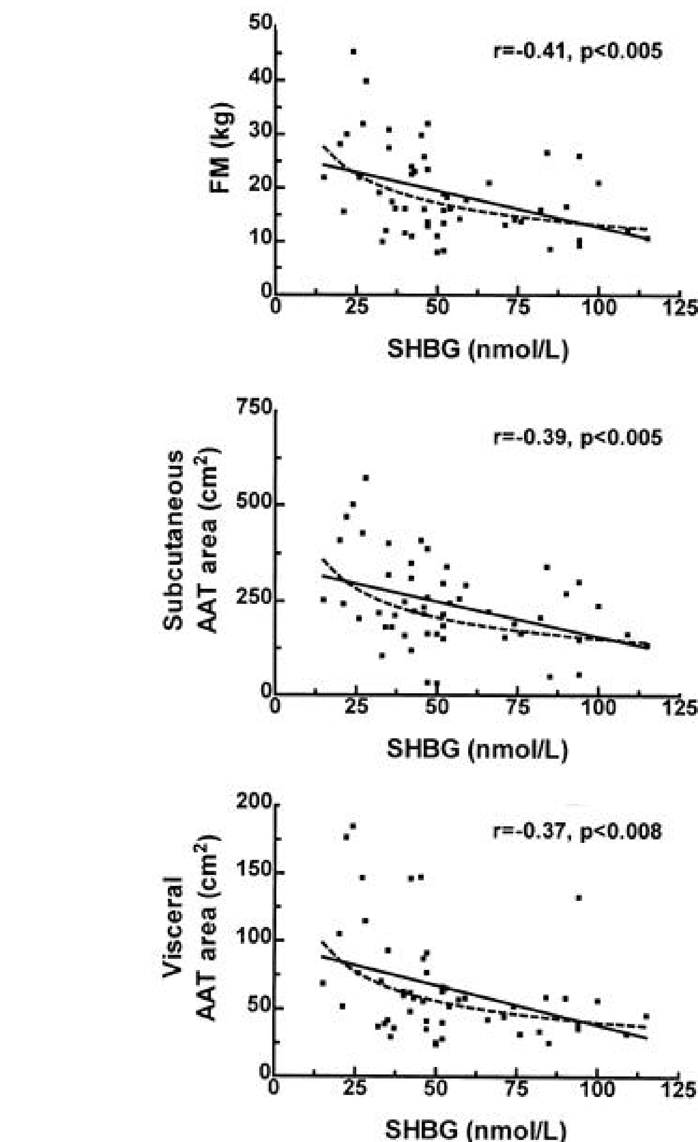

Figure 1—*Correlations between plasma SHBG levels, total body fat mass (FM), subcutaneous abdominal adipose tissue (AAT), and intra-abdominal adipose tissue areas. The* r *value corresponds to the Pearson's coefficient for the linear correlation. Linear (——) and log-log models (- - -) were used to fit data.*

Adjustment for BMI only attenuated these relationships (Table 2). However, these associations were nonsignificant after adjustment for either total body fat mass or visceral adipose tissue area. The relationship between SHBG and cholesterol/HDL cholesterol remained significant after adjustment for total body fat mass. The association between SHBG and HDL cholesterol levels (Fig. 2) was still significant after adjustment for any of the adiposity measures.

We used matching procedures to further examine the relative contribution of SHBG levels and intra-abdominal adipose tissue area to differences in insulin response and HDL cholesterol concentration (Fig. 3). Ten pairs of subjects with either high or low levels of SHBG, but matched for the intra-abdominal fat area, showed no differences in the insulin response to oral glucose. Conversely, when 10 pairs of subjects were matched for SHBG but differed by intra-abdominal fat accumulation, we noted an increased insulin response to oral glucose in women with elevated intra-abdominal fat (Fig. 3*A*). Subjects with high SHBG levels were characterized by higher HDL cholesterol levels compared with subjects with low SHBG, even if subjects were individu-

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Table 2—*Pearson's correlation coefficients between SHBG levels and metabolic variables before and after statistical adjustment for BMI, body fat mass, or intra-abdominal adipose tissue area*

	SHBG			
	Unadjusted	Adjusted for BMI	Adjusted for fat mass	Adjusted for IAF
Glucose/insulin homeostasis				
Fasting insulin*	−0.27†	−0.12	−0.04	−0.10
Fasting glucose	0.04	0.10	0.11	0.11
OGTT insulin AUC*	−0.40‡	−0.29†	−0.20	−0.21
OGTT glucose AUC	−0.23	−0.10	−0.04	−0.05
Insulin/glucose AUC*	−0.36†	−0.29†	−0.21	−0.22
Blood lipid-lipoproteins				
Total cholesterol*	0.03	0.15	0.19	0.22
HDL cholesterol	0.65‡	0.58‡	0.53‡	0.52‡
Triglycerides*	−0.29†	−0.18	−0.12	−0.06
LDL cholesterol*	0.03	0.02	0.19	0.22
Cholesterol/HDL cholesterol*	−0.51‡	−0.36†	−0.29†	−0.25

IAF, intra-abdominal fat area. *Log_{10} transformed values were used for these variables; †$P \leq 0.05$; ‡$P < 0.005$.

ally matched for intra-abdominal fat area. Subjects with high intra-abdominal fat also had lower HDL cholesterol concentrations compared with subjects with low levels of intra-abdominal fat, despite matching for SHBG levels (Fig. 3*B*). Results were similar when total body fat mass was used as a matching variable (results not shown).

Plasma total testosterone levels and the free androgen index were also examined (not shown). Testosterone levels were not significantly associated with adiposity measures or metabolic variables. On the other hand, the association pattern found between the free androgen index (testosterone/SHBG × 100) and adiposity and metabolic profile was not different from the one obtained with SHBG concentrations alone (results not shown).

CONCLUSIONS — We tested the hypothesis that an elevated intra-abdominal adipose tissue accumulation and body fatness mediated part of the association between low SHBG levels and an altered metabolic profile. The major finding is that direct measures of both intra-abdominal adipose tissue accumulation (computed tomography) and total body fat mass (DEXA) explain the relationship between low SHBG and an altered lipid-lipoprotein profile and insulin/glucose homeostasis in middle-aged premenopausal women.

It is unclear whether the relationship between SHBG and various measures of type 2 diabetes or cardiovascular risk is independent of total and regional adiposity (7,9,16,24). The results of the present study are concordant with previous investigators who showed that adjustments for crude measures of adiposity, such as BMI, only attenuated the relationship (7,9,16). A study by Ivandic et al. (24) also showed that BMI and WHR were more important determinants of insulin response to oral glucose than were SHBG and sex hormone levels in obese premenopausal women. In this study, we found that total or intra-abdominal adiposity mediated an important part of the relation between low SHBG and an altered metabolic profile, using matching or partial correlation approaches.

Interestingly, from a statistical standpoint, the associations between SHBG and adiposity measures (Fig. 1) could be explained by either a linear or a curvilinear model. From a physiological standpoint, a case could be made that below a certain level of SHBG, more interindividual variation in adiposity is observed. However, the cross-sectional nature of this study and its limited sample size preclude firm conclusions in that respect. More studies are needed to elucidate the form of the relationship between SHBG and adiposity.

The importance of overall and intra-abdominal adiposity measures found in the present study may be related to the strong interrelationship among adiposity, glucose intolerance, and an altered cardiovascular disease risk profile. Indeed, obesity, especially in the presence of elevated intra-abdominal adipose tissue accumulation, is related to a cluster of metabolic complications that increase the risk for cardiovascular disease and type 2 diabetes (15,25). Mechanisms to explain this relationship may relate to the anatomical location of the adipose tissue depot. Adipose tissue located within the abdominal cavity releases high levels of fatty acids into the portal circulation, which may in turn impair hepatic metabolism (26). Increased delivery of free fatty acids to the liver is associated with reduced hepatic insulin clearance (27,28), increased production of triglyceride-rich lipoproteins (VLDL), and hepatic glucose production by the liver (29,30). These phenomena may contribute to the dyslipidemic state frequently observed in visceral obesity and may also partially explain altered glucose tolerance of visceral obese patients (30). On the other hand, several cross-sectional (11–13) and weight-loss intervention studies in women (31,32) have shown that SHBG is closely associated

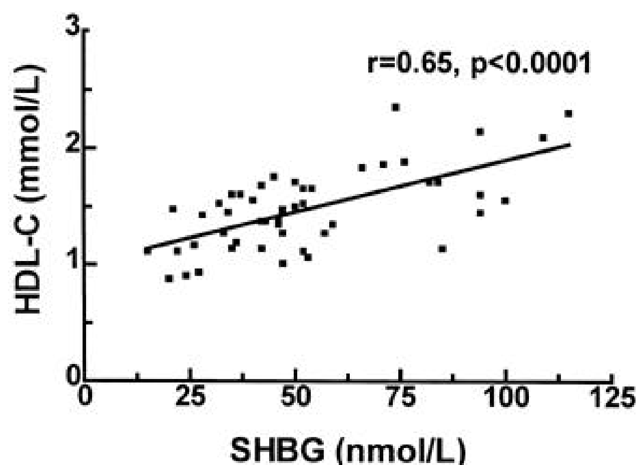

Figure 2—*Correlation between plasma SHBG levels and HDL cholesterol (HDL-C) concentrations.*

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with adipose tissue accumulation. Cross-sectional studies demonstrated that low SHBG levels were associated with increased total and central adiposity (11–13). In the study by Turcato et al. (31), weight loss induced by a very low energy diet increased SHBG levels in premenopausal women. Similarly, Leenen et al. (32) showed that increases in SHBG levels in response to weight reduction were significantly associated with reductions in intra-abdominal adipose tissue accumulation as measured by computed tomography.

Other mechanisms may also explain the relationship noted between SHBG and glucose/insulin homeostasis indices. For example, an in vitro study from Plymate et al. (33) showed a direct effect of insulin on hepatic SHBG secretion. Accordingly, an in vivo study by Nestler et al. (34) showed that suppression of insulin release by diazoxide treatment for 10 days induced significant increases in SHBG levels during an oral glucose load in women with polycystic ovary syndrome. In the present study, we found a significant univariate relationship between SHBG, fasting insulin, and post-glucose insulin response that was no longer significant after adjustment for adiposity measures. Thus, our results do not support an association between hyperinsulinemia and SHBG after control for adiposity. The present design cannot address causality issues and exclude these latter possible mechanisms. However, we would suggest that individual differences in total and regional adiposity mediate an important part of the relationship between low SHBG and glucose and insulin homeostasis indices and plasma lipids. These results are particularly striking when one considers the apparently healthy nature of our population, who displayed normal levels of body fatness and a favorable metabolic profile.

We found that HDL cholesterol was an independent predictor of plasma SHBG concentrations, even after statistical control for total body fat mass or measures of fat distribution. As shown by the matching procedure (Fig. 3*B*), women with low SHBG levels were characterized by lower HDL cholesterol concentrations compared with subjects with high SHBG levels, regardless of their level of intra-abdominal adipose tissue. Conversely, subjects with high intra-abdominal adipose tissue areas had lower HDL cholesterol, independent of SHBG levels (Fig. 3*B*). These results suggest that both intra-abdominal adipose tissue area and SHBG levels independently contribute to the variance of HDL cholesterol concentrations. Previous studies have demonstrated similar associations both between central adiposity and HDL cholesterol (14,35) and between SHBG and HDL cholesterol (1,8,9).

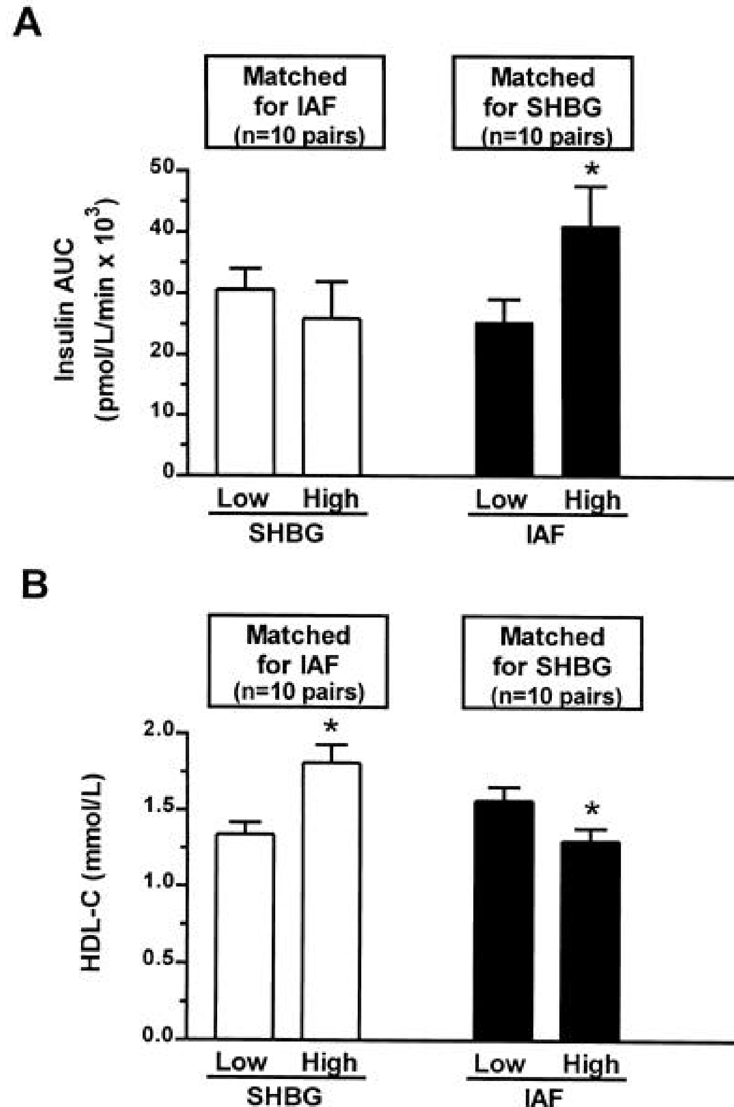

Figure 3—*Comparison of insulin AUC in response to oral glucose (A) and HDL cholesterol (HDL-C) concentration (B) in 10 pairs of women with high or low SHBG (83.5 ± 7.0 vs. 34.8 ± 3.5 nmol/l,* $P < 0.0001$*) but matched for similar levels of intra-abdominal fat (IAF) (56.9 ± 9.2 vs. 157.2 ± 10.7 cm², NS) and in 10 pairs of women with high or low intra-abdominal fat (101.2 ± 9.8 vs. 40.2 ± 4.1,* $P < 0.0001$*) but matched for similar concentrations of SHBG (48.1 ± 5.9 vs. 48.4 ± 5.9 nmol/l, NS); **$P < 0.05$.

The mechanisms underlying the independent association between SHBG and HDL cholesterol concentrations remain unclear. It has been suggested that it may be mediated through the biosynthesis of hepatic lipase (1). According to this hypothesis, SHBG would act as a modulator of hepatic lipase synthesis through the regulation of the balance between androgens and estrogens, which stimulate and inhibit lipase synthesis, respectively (1). Presumably, this phenomenon would be independent of concomitant variation in adiposity and, therefore, may potentially explain findings of the present study.

Several limitations of the present study should be acknowledged. First, the cross-sectional design of this study does not provide information as to the directionality of the associations. Thus, it is not possible to delineate causal relationships from this analysis. Second, SHBG is

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considered a marker of androgenicity in women. It is possible that the associations we found in the present sample reflect the androgen/estrogen balance or free testosterone levels, which were not measured in the present study. Third, the use of the OGTT may allow one to detect large, but not small, differences in glucose tolerance or in the magnitude of the hyperinsulinemic response to a glucose load. Thus, it is possible that we underestimated the contribution of SHBG to hyperinsulinemia in the present study.

In summary, we found that the previously reported relationship between low SHBG levels and increased metabolic disease risk is mediated, to a large extent, by concomitant variation in body fatness and intra-abdominal adipose tissue accumulation measured directly in middle-aged premenopausal women. In this regard, SHBG level may be viewed as a reflection of total and regional adiposity rather than a predictor of an altered insulin/glucose homeostasis. We also found that low SHBG levels were independently associated with reduced HDL cholesterol levels, supporting the notion of a direct link between SHBG and this important marker of cardiovascular disease risk.

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References

1. Pugeat M, Moulin P, Cousin P, Fimbel S, Nicolas MH, Crave JC, Lejeune H: Interrelations between sex hormone-binding globulin (SHBG), plasma lipoproteins and cardiovascular risk. *J Steroid Biochem Mol Biol* 53:567–572, 1995
2. Haffner SM, Valdez RA, Morales PA, Hazuda HP, Stern MP: Decreased sex hormone-binding globulin predicts noninsulin-dependent diabetes mellitus in women but not in men. *J Clin Endocrinol Metab* 77:56–60, 1993
3. Lindstedt G, Lundberg PA, Lapidus L, Lundgren H, Bengtsson C, Björntorp P: Low sex-hormone-binding globulin concentration as an independent risk factor for development of NIDDM. *Diabetes* 40:123–128, 1991
4. Pasquali R, Casimirri F, Plate L, Capelli M: Characterization of obese women with reduced sex hormone-binding globulin concentrations. *Horm Metab Res* 22:303–306, 1990
5. Haffner SM, Katz MS, Stern MP, Dunn JF: The relationship of sex hormones to hyperinsulinemia and hyperglycemia. *Metabolism* 37:683–688, 1988
6. Preziosi P, Barrett-Connor E, Papoz L, Roger M, Saint-Paul M, Nahoul K, Simon D: Interrelation between plasma sex hormone-binding globulin and plasma insulin in healthy adult women: the Telecom study. *J Clin Endocrinol Metab* 76:283–287, 1993
7. Goodman-Gruen D, Barrett-Connor E: Sex hormone-binding globulin and glucose tolerance in postmenopausal women: the Rancho Bernardo Study. *Diabetes Care* 20: 645–649, 1997
8. Soler JT, Folsom AR, Kaye SA, Prineas RJ: Associations of abdominal adiposity, fasting insulin, sex hormone binding globulin, and estrone with lipids and lipoproteins in postmenopausal women. *Atherosclerosis* 79:21–27, 1989
9. Haffner SM, Katz MS, Stern MP, Dunn JF: Association of decreased sex hormone binding globulin and cardiovascular risk factors. *Arteriosclerosis* 9:136–143, 1989
10. Goodman-Gruen D, Barrett-Connor E: A prospective study of sex hormone-binding globulin and fatal cardiovascular disease in Rancho Bernardo men and women. *J Clin Endocrinol Metab* 81:2999–3003, 1996
11. Haffner SM, Katz MS, Dunn JF: Increased upper body and overall adiposity is associated with decreased sex hormone binding globulin in postmenopausal women. *Int J Obes* 15:471–478, 1991
12. Raison J, Bonithon-Kopp C, Egloff M, Ducimetière P, Guy-Grand B: Hormonal influences on the relationships between body fatness, body fat distribution, lipids, lipoproteins, glucose and blood pressure in French working women. *Atherosclerosis* 85:185–192, 1990
13. Evans DJ, Hoffmann RG, Kalkhoff RK, Kissebah AH: Relationship of androgenic activity to body fat topography, fat cell morphology, and metabolic aberrations in premenopausal women. *J Clin Endocrinol Metab* 57:304–310, 1983
14. Després JP, Moorjani S, Ferland M, Tremblay Y, Lupien PJ, Nadeau A, Pinault S, Thériault G, Bouchard C: Adipose tissue distribution and plasma lipoprotein levels in obese women: importance of intra-abdominal fat. *Arteriosclerosis* 9:203–210, 1989
15. Kissebah AH, Krakower GR: Regional adiposity and morbidity. *Physiol Rev* 74:761–811, 1994
16. Peiris AN, Sothmann MS, Aiman EJ, Kissebah AH: The relationship of insulin to sex hormone-binding globulin: role of adiposity. *Fertil Steril* 52:69–72, 1989
17. Starling RD, Toth MJ, Matthews DE, Poehlman ET: Energy requirements and physical activity of older free-living African-Americans: a doubly labeled water study. *J Clin Endocrinol Metab* 83:1529–1534, 1998
18. Tchernof A, Starling RD, Walston JD, Shuldiner AR, Dvorak RV, Silver K, Matthews DE, Poehlman ET: Obesity-related phenotypes and the β_3-adrenoceptor gene variant in postmenopausal women. *Diabetes* 48:1425–1428, 1999
19. Spayd RW, Bruschi B, Burdick BA, Dappen GM, Eikenberry JN, Esders TW, Figueras J, Goodhue CT, LaRossa DD, Nelson RW, Rand RN, Wu TW: Multilayer film elements for clinical analysis: applications to representative chemical determination. *Clin Chem* 24:1348–1350, 1978
20. Allain CC, Poon LS, Chan CSG, Richmond W, Fu PC: Enzymatic determination of total serum cholesterol. *Clin Chem* 20:470–475, 1974
21. Finley PR, Shifman RB, Williams RJ, Lichti DA: Cholesterol in high-density lipoproteins: use of Mg^{2+} dextran sulfate in its enzymatic measurement. *Clin Chem* 24:931–933, 1978
22. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma without the use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
23. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 269:3015–3023, 1993
24. Ivandic A, Prpic-Krizevac I, Sucic M, Juric M: Hyperinsulinemia and sex hormones in healthy premenopausal women: relative contribution of obesity, obesity type, and duration of obesity. *Metabolism* 47:13–19, 1998
25. Kissebah AH, Freedman DS, Peiris AN: Health risks of obesity. *Med Clin North Am* 73:111–138, 1989
26. Björntorp P: "Portal" adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. *Arterisocler Thromb* 10:493–496, 1990
27. Hennes MM, Shrago E, Kissebah AH: Receptor and postreceptor effects of free fatty acids (FFA) on hepatocyte insulin dynamics. *Int J Obes* 14:831–841, 1990
28. Svedberg J, Björntorp P, Smith V, Lonnroth P: FFA inhibition of insulin binding, degradation, and action in isolated hepatocytes. *Diabetes* 39:570–574, 1990
29. Després JP: Obesity and lipid metabolism: relevance of body fat distribution. *Curr Opin Lipidol* 2:5–15, 1991
30. Després JP, Marette A: Relation of components of insulin resistance syndrome to coronary disease risk. *Curr Opin Lipidol* 5:

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274–289, 1994

31. Turcato E, Zamboni M, de Pergola G, Armellini F, Zivelonghi A, Bergamo-Andreis IA, Giorgino R, Bosello O: Interrelationships between weight loss, body fat distribution and sex hormones in pre- and postmenopausal obese women. *J Intern Med* 241:363–372, 1997
32. Leenen R, van der Kooy K, Seidell JC, Deurenberg P, Koppeschaar HP: Visceral fat accumulation in relation to sex hormones in obese men and women undergoing weight loss therapy. *J Clin Endocrinol Metab* 78:1515–1520, 1994
33. Plymate SR, Matej LA, Jones RO, Friedl KE: Inhibition of sex hormone-binding globulin production in the human hepatoma (Hep G2) cell line by insulin and prolactin. *J Clin Endocrinol Metab* 67:460–464, 1988
34. Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Rittmaster RS, Clore JN, Blackard WG: A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. *J Clin Endocrinol Metab* 72:83–89, 1991
35. Fonong T, Toth MJ, Ades PA, Katzel LI, Calles-Escandon J, Poehlman ET: Relationship between physical activity and HDL-cholesterol in healthy older men and women: a cross-sectional and exercise intervention study. *Atherosclerosis* 127:177–183, 1996

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