Relationship Between Sex Hormone–Binding Globulin Levels and Features of the Metabolic Syndrome

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Previous studies have demonstrated that reduced plasma levels of sex hormone–binding globulin (SHBG) are related to alterations in several features of the metabolic syndrome in both men and women. We investigated whether SHBG level was a global predictor of the metabolic syndrome in a sample of 203 men, 173 premenopausal, and 46 postmenopausal women for whom we also obtained a detailed assessment of the metabolic profile, including body composition (hydrostatic weighing), abdominal adipose tissue areas (computed tomography), plasma lipid-lipoprotein levels, and glucose homeostasis (oral glucose challenge). Low SHBG levels were associated with increased total and abdominal adiposity in men as well as in pre- and postmenopausal women. Low SHBG levels were also associated with an altered metabolic profile, especially in premenopausal women. Subjects were subdivided according to the presence of 0, 1 to 2, or 3 or more features of the metabolic syndrome. Twenty-five percent of men were characterized by 3 features or more, whereas most premenopausal women (61.3%) had a healthy metabolic profile (0 features) and 6.9% were characterized by 3 or more features. Most postmenopausal women (54.3%) were characterized by 1 to 2 components of the metabolic syndrome, and 13.0% were characterized by 3 or more components. The proportion of subjects characterized by the metabolic syndrome (3 components or more) was lower in subjects with SHBG values in the upper tertile compared with the lower tertile in both men and premenopausal women (17.7% *v* 28.4% and 1.7% *v* 14.0%, respectively). Logistic regression analyses indicated that an SHBG level in the upper tertile was associated with a significant reduction in the probability of being characterized by the metabolic syndrome (odds ratios of 0.35, *P* = .02 for men and .11, *P* = .05 for premenopausal women, with the lower tertile as a reference). The logistic regression was not significant in postmenopausal women. These results suggest that plasma SHBG level may represent a significant predictor of the metabolic syndrome in men and premenopausal women.

SEX HORMONE–BINDING globulin (SHBG) is a 42-kd circulating glycoprotein involved in the transport of sex steroids,[1] its concentration being a major determinant of their distribution between the protein-bound and free states.[1,2]

Low plasma SHBG levels have been associated with alterations in several components of the metabolic syndrome in both men and women.[3-6] Specifically, low SHBG levels have been associated with increased total and abdominal adiposity,[3,7] hyperinsulinemia, glucose intolerance or insulin resistance,[8-10] and alterations in the lipid profile, including increased triglyceride levels and reduced high-density lipoprotein (HDL)-cholesterol.[3,7,11,12] Accordingly, SHBG levels have been shown to be significant predictors of diabetes development[13] and cardiovascular disease events in some,[14] but not all prospective studies.[15] Given the fact that SHBG secretion may be modulated by several hormonal parameters, such as the androgen/estrogen balance, glucocorticoids,[2,16] and insulin,[17] as well as nutritional factors,[18,19] we and others have previously suggested that elevated plasma SHBG levels may represent a marker for the presence of a low risk, favorable metabolic profile.[3,6] However, to our knowledge, no study has examined whether SHBG level could represent a global predictor of the metabolic syndrome.

In the present study, we investigated whether plasma SHBG level was a significant predictor of the features of the metabolic syndrome in a sample of 203 men and 219 women from the Quebec Family Study (QFS) for whom detailed measures of body composition, body fat distribution, as well as measures of the metabolic profile and SHBG concentrations, were available.

SUBJECTS AND METHODS

Subjects

Subjects of this study were part of the QFS cohort, which includes individuals from French-Canadian families living in and around Québec City recruited through the media for genetic epidemiology, association, and sib-pair linkage studies. For the present study, complete data were available for 203 men aged 42.5 ± 15.0 years and 219 women aged 38.7 ± 12.6 years. All patients were nonsmokers. None of the women had had a polycystic ovary syndrome diagnosis before entering the study. Moreover, only 1 woman was characterized by an SHBG level lower than the recently established polycystic ovary syndrome decision threshold for epidemiological studies (<37 nmol/L).[20] Forty-eight women reported cessation of menstruation for more than a year at physical examination and were, therefore, considered postmenopausal. Postmenopausal women reporting the use of hormone replacement therapy were excluded from this study. Six premenopausal women reported oral contraceptive use and were excluded from the analyses. Patients using medication that could have affected parameters of the metabolic syndrome were excluded from the analysis. All participants were asked to sign an informed consent document, and the study was approved by the Medical Ethics Committee of Laval University.

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Body Composition and Anthropometry

Body composition was measured as previously described[21] by the hydrostatic weighing technique using helium dilution for residual lung volume measurement. The mean of 6 measurements was used in the calculation of body density. Total body fat mass was derived from body density by using the equation of Siri.[22] Body weight and height were measured using standardized procedures.[23]

Computed Tomography

Body fat distribution measures were performed on a Siemens Somatom DRH scanner (Erlanger, Germany) as previously described.[24] Scans were performed at the abdominal level (L4 to L5 vertebrae) using a radiograph of the skeleton as a reference to establish the position of the scan. Total, subcutaneous, and intra-abdominal adipose tissue areas were calculated by delineating tissue surfaces as described[24] and by using an attenuation range of −190 to −30 Hounsfield units.[25]

Metabolic Variables

A 75-g oral glucose tolerance test was performed in the morning after an overnight fast. Blood samples were collected in EDTA and Trasylol (Miles Pharmaceuticals, Rexdale, Ontario, Canada) through a venous catheter at −15, 0, 30, 45, 60, 90, 120, 150, and 180 minutes after glucose ingestion. Plasma glucose was measured enzymatically, and insulin was measured by radioimmunoassay with polyethylene glycol separation. The glucose and insulin areas under the curve during the oral glucose tolerance test were determined with the trapezoid method. The homeostasis model assessment (HOMA) was used to calculate the insulin resistance index.[26] Cholesterol and triglyceride levels were determined in plasma and lipoprotein fractions using a Technicon RA-500 analyzer (Bayer, Tarrytown, NY). Plasma very–low-density lipoprotein (VLDL) was isolated by ultracentrifugation, and the HDL fraction was obtained after precipitation of low-density lipoprotein (LDL) in the infranatant with heparin and $MnCl_2$.[27] The HDL_2 and HDL_3 subfractions were obtained by precipitation. Apolipoprotein B levels were determined in plasma and lipoprotein fractions according to the method of Laurell.[28] Plasma SHBG levels were measured in duplicate by radioimmunoassay (Diagnostic Systems Laboratories, Webster, TX). Intra- and interassay coefficients of variation were 2.55% and 5.93%, respectively.

Statistical Analyses

Data are presented as mean ± SD. Patients were subdivided according to gender and menopausal status. Analysis of variance was performed for variables with homogeneous variances, whereas the Welch analysis of variance[29] was used with variables for which the homogeneity of variance assumption was rejected by Levene's test. Group differences were tested using least square means contrasts. Spearman correlation coefficients were computed to quantify the magnitude of the association between plasma SHBG levels and variables of the metabolic profile. The number of components of the metabolic syndrome was established for each participant according to the following criteria[30-33]: visceral adipose tissue area ≥ 130 cm^2, systolic blood pressure ≥ 140 mm Hg, plasma triglycerides > 1.69 mmol/L, HDL-cholesterol < 1.00 mmol/L, and fasting glycemia ≥ 6.1 mmol/L. Ten participants were diabetic and 36 were glucose intolerant, 28 were hypertensive, 132 were abdominally obese, and 201 were characterized by either high blood cholesterol, high triglycerides, or low HDL-cholesterol levels. Subjects were subdivided into 3 categories according to the number of metabolic syndrome features: 0, 1 to 2, or 3 and more. The presence of 3 components or more was defined as the metabolic syndrome.[34] SHBG tertiles were determined within each subgroup taken separately (men, premenopausal women, and postmenopausal women). Frequencies of subjects in each category of metabolic syndrome components and each SHBG tertile were compared with the χ^2 test. Logistic regression analysis was used to determine the probability of being characterized by 3 or more features of the metabolic syndrome in each SHBG tertile. Age was included in all models. Significance level was established at $P \leq .05$. Analyses were performed using JMP statistical analysis software (SAS Institute, Cary, NC).

RESULTS

Table 1 shows physical characteristics of the study sample. Based on body mass index (BMI) values, men as well as pre- and postmenopausal women were overweight on average (BMI ≥25 kg/m^2). However, BMI values covered a wide range (from 17.9 to 45.7 kg/m^2 for men and from 16.8 to 49.9 kg/m^2 for women). Premenopausal women were significantly younger than men and postmenopausal women. Premenopausal women were also characterized by lower intra-abdominal adipose tissue areas compared with both men and postmenopausal women. No significant difference in intra-abdominal adipose tissue area was noted between men and postmenopausal women. Accordingly, premenopausal women were characterized by lower total and LDL-cholesterol levels, increased HDL-cholesterol, as well as lower triglyceride, apolipoprotein B, and fasting glucose levels compared with men and postmenopausal women. No significant difference was noted in fasting insulin or in the response to the oral glucose challenge.

We examined the correlations between plasma SHBG levels and metabolic variables in men as well as pre- and postmenopausal women (Table 2) . Plasma SHBG levels were negatively correlated with BMI, body fat mass, and abdominal adipose tissue areas (subcutaneous and intra-abdominal) in all 3 subgroups. Significant associations were also noted between SHBG and VLDL-cholesterol, HDL_2-cholesterol, and triglyceride levels in men. In premenopausal women, plasma SHBG levels were positively associated with the cholesterol content of the HDL, HDL_2, and HDL_3 subfractions. In premenopausal women only, negative associations were noted between SHBG levels, fasting insulin, insulin resistance (HOMA model), and the fasting insulin/glucose ratio.

The number of components of the metabolic syndrome was computed for each participant and metabolic syndrome categories were established accordingly (see Subjects and Methods for reference values). Figure 1 shows frequencies of subjects characterized by 0, 1 to 2, or 3 or more features of the metabolic syndrome. Whereas 25.1% of men were characterized by 3 or more features of the metabolic syndrome, most premenopausal women (61.3%) were characterized by a healthy metabolic profile, and only 6.9% had 3 or more components of the metabolic syndrome. The majority of postmenopausal women (54.3%) were characterized by 1 or 2 components of the metabolic syndrome, and 13.0% were characterized by 3 or more components.

We then examined frequencies of subjects characterized by 0, 1 to 2, or 3 and more components of the metabolic syndrome in each SHBG tertile (Fig 2). The proportion of subjects with the metabolic syndrome (3 components or more) was 17.7% in

Table 1. Physical Characteristics of Study Sample

	Men	Women	
		Premenopausal	Postmenopausal
Age (y)	42.5 ± 15.0	34.0 ± 9.3‡‖	56.5 ± 5.7‡§
BMI (kg/m^2)	27.0 ± 4.8	26.6 ± 7.2‖	28.7 ± 7.2§
Fat mass (kg)	19.5 ± 10.0	22.3 ± 13.3‡‖	27.7 ± 12.0‡§
SHBG (nmol/L)	58.9 ± 16.2	70.0 ± 21.7‡‖	77.3 ± 29.3‡§
Abdominal AT areas (cm^2)			
Total	346 ± 186	398 ± 229‡‖	507 ± 215‡§
Intra-abdominal	127 ± 75	81 ± 54‡‖	139 ± 56‡§
Subcutaneous	219 ± 130	317 ± 185‡	368 ± 177‡
Lipoprotein profile			
Total cholesterol (mmol/L)	5.01 ± 0.98	4.64 ± 0.87‡‖	5.50 ± 0.75‡§
LDL-cholesterol (mmol/L)	3.21 ± 0.83	2.81 ± 0.76‡‖	3.38 ± 0.74§
VLDL-cholesterol (mmol/L)	0.56 ± 0.40	0.38 ± 0.27‡	0.45 ± 0.20‡
HDL-cholesterol (mmol/L)	1.10 ± 0.28	1.29 ± 0.32‡‖	1.46 ± 0.31‡§
HDL_2-cholesterol (mmol/L)*	0.34 ± 0.18	0.49 ± 0.20†‡	0.58 ± 0.24‡§
HDL_3-cholesterol (mmol/L)*	0.68 ± 0.14	0.70 ± 0.15‡‖	0.77 ± 0.16‡§
Triglycerides (mmol/L)	1.62 ± 1.05	1.20 ± 0.58‡‖	1.48 ± 0.58§
Apolipoprotein B (g/dL)	1.02 ± 0.24	0.89 ± 0.20‡‖	1.06 ± 0.18§
Insulin/glucose homeostasis			
Fasting glucose (mmol/L)	5.5 ± 1.1	5.1 ± 0.70‡	5.3 ± 0.6
Fasting insulin (pmmol/L)	69.1 ± 45.4	69.5 ± 53.5	74.7 ± 72.6
HOMA-IR	17.6 ± 14.0	16.0 ± 13.5	18.2 ± 21.1
INS/GLU	12.4 ± 7.7	13.7 ± 10.8	13.8 ± 11.5
Glucose AUC (mmol/L/min/10^3)†	1.3 ± 0.4	1.1 ± 0.2‡‖	1.3 ± 0.3§
Insulin AUC (pmol/L/min/10^3)†	78.2 ± 57.3	76.4 ± 55.0	89.9 ± 75.6

NOTE. Sample size included 203 men, 173 premenopausal women, and 46 postmenopausal women.

Abbreviation: AUC, area under response curve.

*172 premenopausal women for these measurements; †199 men, 167 premenopausal women, and 44 postmenopausal women for these measurements; ‡different from men ($P < .05$); §different from premenopausal women ($P < .05$); ‖different from postmenopausal women ($P < .05$).

men with elevated SHBG values (upper tertile), whereas 28.4% were characterized by the syndrome in the lower tertile ($P < .009$). Conversely, the proportion of healthy subjects (0 feature) was higher in the upper tertile (42.7%) compared with the lower tertile (20.9%, $P < .009$). In premenopausal women, only 1.7% were characterized by the metabolic syndrome in the upper tertile of SHBG, while the vast majority of these women had no component of the metabolic syndrome (72.4%, $P < .02$). The proportion of women characterized by the metabolic syndrome was also increased in the lower SHBG tertile (14.0%) compared with higher SHBG values ($P < .02$), although most women were characterized by a healthy metabolic profile. The same trend was noted in postmenopausal women. However, the χ^2 analysis generated a nonsignificant P value in this group.

Logistic regression analyses were performed to estimate the probability of being characterized by the metabolic syndrome (3 features or more) according to SHBG tertiles. All models presented in Table 3 included age. Compared with the lower SHBG tertile, significant reductions in the probability of being characterized by the metabolic syndrome were noted in both men (−65%, $P = .02$) and premenopausal women (−89%, $P = .05$) with the highest SHBG levels (upper tertile). No significant reduction in the risk of being characterized by the metabolic syndrome was noted across tertiles of SHBG in postmenopausal women.

DISCUSSION

The analyses presented in this report were prompted by the fact that SHBG levels are associated with a number of metabolic variables, which are also recognized as components of the metabolic syndrome. A recent report from the Third National Health and Nutrition Examination Survey[34] examined a sample of 8,814 men and women and demonstrated that approximately 25% of the population at all ages was characterized by the metabolic syndrome, which was defined as the presence of 3 or more recognized features.[34] This proportion appeared to increase dramatically with aging, as 43% of the population 60 years and older was characterized by the metabolic syndrome.[34] These results suggest that the metabolic syndrome will most likely represent a public health problem of great importance in the future. As mentioned, it is expected that low SHBG levels be correlated with several individual features of this syndrome. However, to our knowledge, no study had examined whether SHBG level could represent a global predictor of the metabolic syndrome.

Several reports have demonstrated significant associations between plasma SHBG levels and variables of the metabolic profile. Low SHBG levels have generally been associated with increased total and abdominal adiposity,[3,7] hyperinsulinemia, glucose intolerance or insulin resistance,[8-10] and alterations in the lipid profile, including increased triglyceride levels and

Table 2. Spearman Rank Correlation Coefficients Between Plasma SHBG Levels and Metabolic Variables in Study Sample

	SHBG		
	Men	Premenopausal Women	Postmenopausal Women
Age	0.20§	−0.07	−0.20§
BMI	−0.21§	−0.35§	−0.21§
Fat mass	−0.20§	−0.36§	−0.20§
Abdominal AT areas			
Total	−0.23§	−0.41§	−0.23§
Intra-abdominal	−0.15‡	−0.38§	−0.15‡
Subcutaneous	−0.26§	−0.41§	−0.26§
Lipoprotein profile			
Total cholesterol	−0.03	−0.11	−0.03
LDL-cholesterol	0.02	−0.15‡	−0.02
VLDL-cholesterol	−0.25§	−0.08	−0.25§
HDL-cholesterol	0.15‡	0.17‡	0.15‡
HDL_2-cholesterol*	0.22§	0.13‖	0.22§
HDL_3-cholesterol*	−0.01	0.19‡	−0.01
Triglycerides	−0.23§	−0.08	0.23§
Apolipoprotein B	−0.04	−0.10	−0.04
Insulin/glucose homeostasis			
Fasting glucose	−0.11	−0.10	−0.11
Fasting insulin	−0.11	−0.21‡	−0.11
HOMA-IR	−0.11	−0.20‡	−0.11
INS/GLU	−0.11	−0.23§	−0.11
Glucose AUC†	−0.10	−0.12	−0.10
Insulin AUC†	−0.10	−0.12	−0.10

NOTE. Men (n = 203), premenopausal women (n = 173), and postmenopausal women (n = 46).

*172 premenopausal women for these measurements; †199 men, 167 premenopausal women, and 44 postmenopausal women for these measurements; ‡$P < .05$; §$P < .005$; ‖$P < .09$.

reduced HDL-cholesterol.[3,7,11,12] Our results are concordant with these findings, as low SHBG levels were associated with increased total and visceral adiposity in men, as well as in pre- and postmenopausal women. Moreover, SHBG was a significant correlate of an altered lipoprotein-lipid profile in both men and premenopausal women. On the other hand, the association between plasma SHBG and variables of glucose homeostasis were significant in premenopausal women, but not in men of the present study. This is also consistent with discrepancies noted in previous reports. For example, others and we have found the association between SHBG and fasting insulin to be significant,[13,35] while other groups found no correlation.[36] The same is true for the association between SHBG and HDL-cholesterol levels in men, which was found to be significant in some,[15,35] but not all[37] studies. The reasons for these discrepancies are unclear at the present time. However, more frequent study discrepancies can be noted in men, while the correlation pattern between SHBG levels and metabolic variables is much more consistent in women. This may be attributable to the fact that the high total androgen levels of men lead to lower SHBG values and reduced SHBG variance. Accordingly, in the present study, SHBG levels were significantly lower in men compared with women. The variance in SHBG was also significantly lower in men. This gender difference in SHBG variability may have contributed to study differences in the pattern of correlation between SHBG and metabolic variables in men. The associations between plasma SHBG levels and metabolic variables were also of lower magnitude in postmenopausal women compared with their premenopausal counterpart. As a result, SHBG level was not a significant predictor of the metabolic syndrome in this population. We hypothesize that this may be related either to the increased androgen/estrogen ratio noted after menopause, which would lead to smaller variances in SHBG, or to the relatively low sample size of this group (n = 46).

We found that men and premenopausal women with high SHBG levels were generally characterized by fewer features of the metabolic syndrome compared with those with low SHBG levels. These results suggest that plasma SHBG could represent a marker of the metabolic syndrome. However, the association appears to be less than perfect, as a significant proportion of patients with elevated SHBG were characterized by 1, 2, or even more components of the metabolic syndrome. This likely reflects the moderate strength of the correlations observed between SHBG and metabolic variables, and also indicates that other factors unrelated to the metabolic syndrome contribute to the variation in SHBG level. From the clinical standpoint, more studies are required to determine whether SHBG measurement would provide additional meaningful information on the metabolic syndrome compared with already established clinical indicators, such as waist circumference, fasting glycemia, blood pressure measurements, and the lipid profile.

Whether SHBG is a causal agent of the metabolic syndrome or merely represents a marker for primary endocrine abnormalities leading to these metabolic alterations remains unclear at the present time. Although the cross-sectional nature of the present study prevents from concluding on cause-and-effect relationships, available data suggest that SHBG levels are modulated in response to metabolic signals, rather than the opposite. A study by Plymate et al[17] showed a direct inhibiting effect

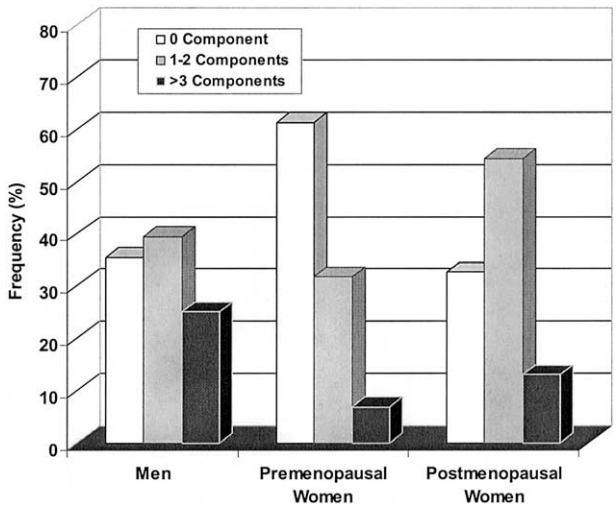

Fig 1. Frequency distribution according to the number of components of the metabolic syndrome (see Subjects and Methods) in men (n = 203), premenopausal women (n = 173), and postmenopausal women (n = 46). χ^2 *P* value < .0001.

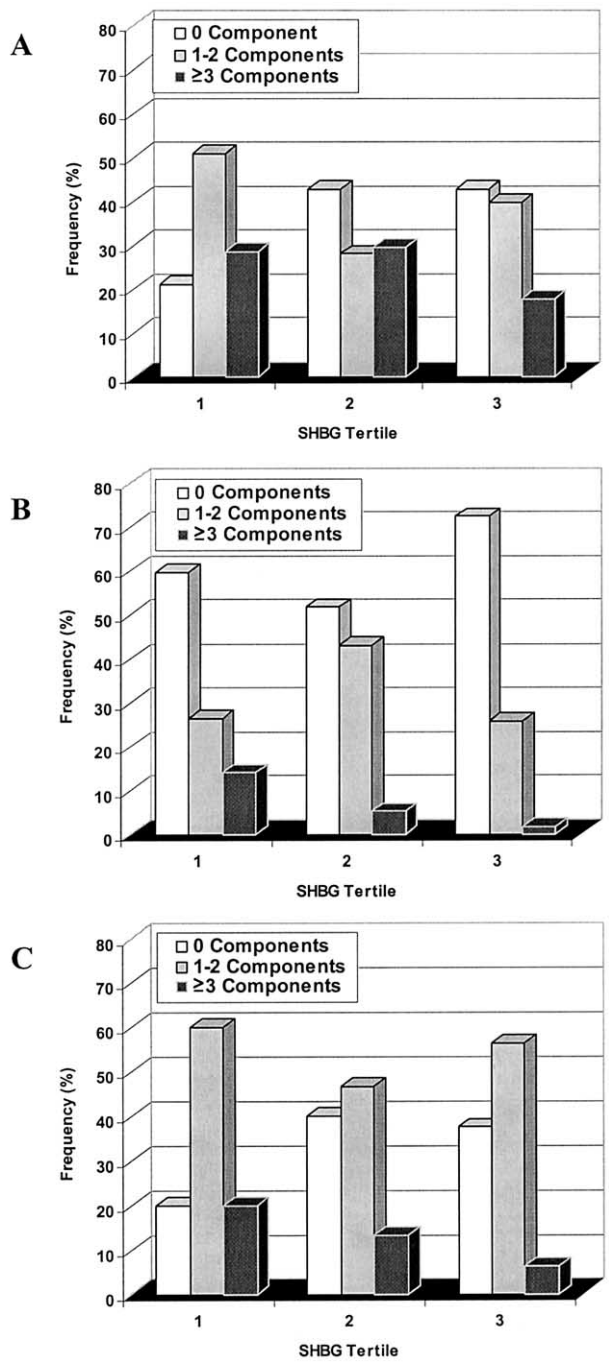

Fig 2. Frequency distribution according to the number of components of the metabolic syndrome and plasma SHBG tertile (see Subjects and Methods) in (A) men (n = 203, χ^2 *P* value < .009); (B) premenopausal women (n = 173, χ^2 *P* value <.02); and (C) postmenopausal women (n = 46, χ^2 *P* value = .62).

of insulin on hepatic SHBG secretion, and Nestler et al[38] 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 the polycystic ovary syndrome. In addition, a study by Lemieux et al[39] demonstrated that the restoration of normal androgen and SHBG levels using laparoscopic ovarian cautery in women with polycystic ovaries did not modulate insulin sensitivity. Although women with polycystic ovary syndrome were excluded from the present study, these results suggest that the presence of this syndrome may mediate the relationship between low SHBG and metabolic alterations.[20,40]

Cortisol also inhibits SHBG production,[2] and patients with abdominal obesity and insulin resistance are characterized by increased local cortisol production in abdominal adipose tissue,[41,42] as well as an increased sensitivity of the hypothalamic-pituitary-adrenal axis.[43] Elevated cortisol production could also lead to the decreased SHBG levels observed in subjects with the metabolic syndrome. Plasma levels of SHBG are also regulated by androgens and estrogens.[2] An increased local conversion of androgens to estrogens in a enlarged adipose tissue mass[44] could also contribute to modulate the androgen/estrogen balance and increase SHBG levels. Finally, several studies have shown that nutritional interventions with low-fat diets or dietary fiber[19,45] and also exercise treatment[46] lead to increased SHBG levels. Whether these changes are primarily mediated by concomitant improvements in insulin sensitivity or cortisol metabolism remains to be determined. Taken together, available literature suggests that several hormonal, metabolic, and nutritional signals may modulate SHBG production in the liver, which would act as an integrated marker for these signals. More studies are needed to confirm this hypothesis.

In summary, consistent with previous studies, we found that

Table 3. Multiple Logistic Regression Analysis of the Probability of Being Characterized by 3 or More Features of the Metabolic Syndrome According to SHBG Tertiles in Study Sample

	β	Odds Ratio	95% CI	*P* Value
Men				
SHBG tertile 1 (14.4-52.8)	0	1.0	—	—
SHBG tertile 2 (53.0-62.7)	−0.05	0.96	0.42-2.18	NS
SHBG tertile 3 (62.8-179.7)	−1.06	0.35	0.13-0.84	.02
Premenopausal women				
SHBG tertile 1 (33.6-56.4)	0	1.0	—	—
SHBG tertile 2 (56.8-75.6)	−1.27	0.28	0.06-1.08	.08
SHBG tertile 3 (75.9-175.2)	−2.21	0.11	0.01-0.67	.05
Postmenopausal women				
SHBG tertile 1 (40.1-60.5)	0	1.0	—	—
SHBG tertile 2 (60.6-75.5)	0.46	1.58	0.22-13.71	NS
SHBG tertile 3 (77.0-170.6)	1.40	4.05	0.43-97.31	NS

NOTE. Men (n = 203), premenopausal women (n = 173), and postmenopausal women (n = 46). Age included in all models; SHBG values in nmol/L.

Abbreviation: NS, not significant; CI, confidence interval.

low plasma SHBG levels were associated with an altered metabolic profile in men and women. Moreover, elevated SHBG levels were associated with a reduced number of features of the metabolic syndrome, especially in men and premenopausal women. Logistic regression analyses demonstrated that elevated SHBG levels might be related to significant reductions in the probability of being characterized by the metabolic syndrome. These results suggest that plasma SHBG level may represent a significant predictor of the metabolic syndrome. It is suggested that SHBG may reflect the integration of several hormonal, metabolic, and nutritional stimuli.

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