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Low sex hormone–binding globulin is associated with the metabolic syndrome in postmenopausal women

Melissa E. Weinberg[a,*], JoAnn E. Manson[a,c], Julie E. Buring[a,c,d], Nancy R. Cook[a], Ellen W. Seely[b], Paul M. Ridker[a], Kathryn M. Rexrode[a]

[a]*Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02215, USA*
[b]*Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA*
[c]*Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA*
[d]*Department of Ambulatory Care and Prevention, Harvard Medical School, Boston, MA 02115, USA*

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Abstract

Although an association between the metabolic syndrome and hyperandrogenism has been suggested in women with polycystic ovarian syndrome, few studies have investigated this relationship in postmenopausal women. We measured estradiol, testosterone, and sex hormone–binding globulin (SHBG) and calculated the free androgen index (FAI) in 212 postmenopausal women not using hormone therapy in the Women's Health Study. A modified definition of the metabolic syndrome (3 or more of the following: abdominal obesity, hypertriglyceridemia, low high-density lipoprotein, elevated blood pressure, and abnormal glucose metabolism) from the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults was used. Women with the metabolic syndrome had higher mean levels of estradiol, testosterone, and FAI values and lower SHBG levels. Higher FAI and lower SHBG were associated with all components of the metabolic syndrome. After adjustment for BMI and other factors, women in the highest tertile of FAI had an odds ratio of 12.6 (95% confidence interval, 3.8-41.6) for the metabolic syndrome, whereas those in the lowest SHBG tertile had an odds ratio of 7.3 (95% confidence interval, 2.7-19.8). When stratified by body mass index, the associations with high FAI and low SHBG remained significant even in women with body mass index less than 26.7 kg/m^2. An androgenic hormone profile is associated with both the individual components of the metabolic syndrome and clustering of metabolic abnormalities in postmenopausal women.

1. Introduction

The metabolic syndrome identifies a cluster of metabolic abnormalities that place affected individuals at increased risk for developing diabetes mellitus [1] and cardiovascular disease (CVD) [2], as well as increased mortality from all causes [3]. The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) provides a clinically useful working definition of the metabolic syndrome that includes the presence of at least 3 of the following characteristics: abdominal obesity, elevated triglycerides, reduced levels of high-density lipoprotein (HDL) cholesterol, high blood pressure, and elevated fasting glucose [4].

An association between the metabolic syndrome and hyperandrogenism has been suggested in premenopausal women with polycystic ovarian syndrome. These women have an increased rate of metabolic abnormalities including central obesity, impaired glucose tolerance or diabetes, hypertension, and dyslipidemia [5,6]. The relationships of both androgens and estrogens with individual features of the metabolic syndrome such as hypertension, insulin resistance, and dyslipidemia have been investigated in both pre- and postmenopausal women [7-16]; however, few studies [17-19] have examined the relationship between

* Corresponding author. Division of Endocrinology, University of California-San Francisco, VA Medical Center, San Francisco, CA 94121, USA. Tel.: +1 415 750 2089; fax: +1 415 750 6929. Reprints: Kathryn M. Rexrode, Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA 02215, USA. Tel.: +1 617 278 0834; fax: +1 617 731 3843.

E-mail addresses: melissa.weinberg@ucsf.edu (M.E. Weinberg), krexrode@partners.org (K.M. Rexrode).

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endogenous sex hormone levels and the metabolic syndrome as recently defined, and these reports have not provided definitive results in postmenopausal women.

Whether the association between sex hormones and the metabolic syndrome observed in premenopausal women persists through menopause has important public health implications because the prevalence of both the metabolic syndrome [20] and CVD increase after menopause. We examined the relationship of sex hormones and sex hormone–binding globulin (SHBG) with the metabolic syndrome in a cross-sectional analysis of a nested case-control study of women in the Women's Health Study (WHS).

2. Materials and methods

2.1. Participants

The relationship of endogenous sex hormones and the metabolic syndrome was evaluated among a subset of postmenopausal women participating in the WHS, an ongoing randomized, double-blind, placebo-controlled study of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer [21]. Apparently healthy women with no known CVD or cancer (except nonmelanoma skin cancer) were enrolled between November 1992 and July 1995. Among the 39 876 female health professionals age 45 years or older at baseline randomized into the study, 28 345 (71%) provided baseline fasting blood samples, which were stored in liquid nitrogen freezers at −170°C until the time of analysis.

Data on traditional cardiac risk factors were gathered in the WHS at baseline. WHS participants complete yearly questionnaires on demographic, behavioral, and lifestyle factors, as well as the occurrence of any medical illnesses. They were also asked to consent to release of relevant medical records, which are reviewed by an end point committee of physicians. Postmenopausal status was defined by the report of no menses for more than 12 months in the presence of natural menopause or at the time of bilateral salpingoophorectomy. Women who had undergone hysterectomy with either one or no ovaries removed were considered postmenopausal at age 56 (the age by which 95% of the cohort reached natural menopause).

For the current analysis, we used sex hormone values from a prior case-control study of 200 postmenopausal women who developed CVD and 200 control subjects [22]. Our analysis excluded all subjects who were currently using hormone therapy because exogenous hormone use has dramatic effects on levels of the endogenous hormones studied [22]. Of the 230 women remaining, 6 participants were excluded because of unclear menopausal status. Twelve additional women were excluded because one or more variables in the metabolic syndrome definition were missing, leaving 212 women for our analyses. All participants were free from known CVD at baseline when the blood samples were collected. A composite end point of CVD, defined as the first occurrence of nonfatal myocardial infarction (MI), coronary revascularization, nonfatal stroke, coronary disease, or stroke death, was used in the primary study [22].

2.2. Sex hormone assays

All hormone assays were conducted in 2000. Total estradiol levels were measured at Quest Diagnostics (Capistrano, CA) by radioimmunoassay (RIA) preceded by extraction and purification by Celite column chromatography. The lower limit of detection for the assay was 5 pg/mL. Total testosterone and SHBG levels were assayed at the Massachusetts General Hospital Reproductive Endocrine Laboratory (Boston, MA). Testosterone was measured by using a solid-phase RIA (Diagnostic Products, Los Angeles, CA). Because all testosterone measurements were above the lower limit of detection of 4.0 ng/dL, the extraction method was not necessary. SHBG was measured by using a fully automated system (Immunolite; Diagnostic Products), which used a solid-phase, two-site immunometric assay. Coefficients of variation from interspersed quality-controlled specimens were 9.5% for estradiol, 4.8% for testosterone, and 4.5% for SHBG. To estimate free (non–protein-bound) testosterone, we calculated the free androgen index (FAI), the molar ratio of total testosterone/SHBG multiplied by 100, which is highly correlated with free testosterone [23,24].

2.3. Definition of the metabolic syndrome

According to the ATP III guidelines, the metabolic syndrome for women is defined as having 3 or more of the following: (1) abdominal obesity identified by a waist circumference greater than 88 cm; (2) triglyceride levels of 150 mg/dL or greater; (3) HDL cholesterol level less than 50 mg/dL; (4) blood pressure of 130/85 mm Hg or higher; and (5) abnormal glucose metabolism as identified by a fasting blood glucose level of 110 mg/dL or higher [4]. A modified ATP definition, validated in prior work in the WHS [25], was used.

2.3.1. Obesity

Because waist circumference was not available at baseline, a cutpoint for obesity of body mass index (BMI) of 26.7 kg/m^2 or higher was used as a surrogate. This value corresponded to the same percentile for BMI as did a waist circumference of 88 cm when it was measured at year 6 of follow-up. Self-reported values for height and weight were used to calculate BMI. In a validation study of weight among 184 women in a similar cohort of female health professionals, the measured weights averaged only 1.5 kg (corresponding to an average difference in BMI of 0.5 kg/m^2) higher than the self-reported weights with a Spearman correlation of 0.96 [26].

2.3.2. Triglycerides and HDL cholesterol

Triglyceride and HDL cholesterol levels were directly measured by using stored baseline blood samples (Roche Diagnostics, Indianapolis, IN).

Table 1
Baseline characteristics of women with and without metabolic syndrome

Characteristic	Women with metabolic syndrome (n = 108)	Women without metabolic syndrome (n = 104)	P
Mean age (y)	63.9	65.8	.03
Mean age at menopause (y)	47.2	47.7	.56
Mean BMI (kg/m^2)	28.6	23.8	<.001
Smoking (%)			
Never	38.0	38.5	.94
Past	40.7	40.4	.96
Current	21.3	21.2	.98
Physical activity (%)			
Rarely/never	57.4	47.1	.13
<1-3/wk	35.2	38.5	.62
≥4/wk	7.4	14.4	.10
Alcohol consumption			
Rarely/never	56.5	51.9	.51
1-3 /mo	13.9	11.5	.61
>1 /wk	29.6	36.5	.28
History of oophorectomy (%)	20.4	13.5	.18
Parental history of MI (%)[a]	15.7	10.4	.27
Developed CVD during follow-up (%)	63.0	37.5	.0002

[a] History of MI in either or both parents before age 60 years.

2.3.3. Elevated blood pressure

Subjects with elevated blood pressure included those who reported a diagnosis of hypertension by a clinician on either the baseline or the run-in questionnaires. Those reporting systolic blood pressure (SBP) of 130 mm Hg or higher or diastolic blood pressure (DBP) of 85 mm Hg or higher on the run-in questionnaire (if blood pressure had been measured during the previous 2 years, chosen from 9 categories for SBP and 7 categories for DBP) were also included. A single measurement of self-reported blood pressure has been shown to be highly correlated with measured SBP (r = 0.72) and DBP (r = 0.60) in health professionals [27].

2.3.4. Glucose intolerance

Because fasting glucose levels were not available, we used the diagnosis of diabetes at either baseline or during follow-up to identify individuals with baseline impairment of glucose metabolism. The diagnosis of diabetes was determined by self-report on the basis of annual questionnaires. The validity of self-reported diabetes has been shown in the WHS [28]. This modified ATP definition has been previously used in the WHS and has been shown to predict cardiovascular events [25].

2.4. Statistical analysis

Because hormone levels were skewed, continuous values were log-transformed to achieve normality. Geometric means of baseline endogenous hormones, adjusted for age and CVD case-control status, were compared by the general linear model procedure for the metabolic syndrome and each of its components. To assess potential confounding and effect modification, geometric mean hormone levels were additionally compared within strata of BMI (<26.7 and ≥26.7 kg/m^2) for those with and without the metabolic syndrome. In addition, we classified all subjects as having 0, 1, 2, 3, or more components of the metabolic syndrome and assessed for a trend across the groups by using general linear model procedure. Additional analyses were performed stratified according to the presence or absence of CVD during follow-up. The stratified analyses yielded similar results in women who remained free of CVD and those who developed CVD during follow-up; therefore, we present primary results on the entire group of 212 women. However, as results tended to be more significant in women who later developed CVD, analyses were adjusted for the subsequent development of CVD.

Table 2
Geometric mean levels of endogenous hormones according to the presence or absence of the metabolic syndrome and each individual component of the metabolic syndrome, adjusted for age and the presence or absence of CVD during follow-up

	Estradiol (pg/mL)	Testosterone (ng/dL)	SHBG (nmol/L)	FAI
Metabolic syndrome				
Yes	12.2	22.7	32.6	2.5
No	9.2	15.9	55.8	1.0
P	.001	<.0001	<.0001	<.0001
Triglycerides (mg/dL)				
≥150	11.1	20.0	34.3	2.0
<150	10.1	18.2	53.4	1.1
P	.26	.28	<.0001	<.0001
HDL (mg/dL)				
<50	11.1	20.9	36.9	2.0
≥50	9.8	16.0	55.9	1.0
P	.19	.003	<.0001	<.0001
Blood pressure (mm Hg)				
≥130/85	11.1	20.4	39.3	1.4
<130/85	9.8	17.0	48.8	1.2
P	.17	.05	.006	.002
BMI (kg/m^2)				
≥26.7	12.8	21.4	34.0	2.2
<26.7	9.0	17.1	52.4	1.1
P	<.0001	.01	<.0001	<.0001
Abnormal glucose metabolism				
Yes	13.0	22.5	29.1	2.7
No	10.1	18.3	46.8	1.4
P	.02	.07	<.0001	<.0001
Stratified by BMI				
BMI <26.7 kg/m^2				
Metabolic Syndrome				
Yes	10.3	22.6	38.1	2.0
No	8.5	15.4	60.0	0.9
P	.22	.01	<.0001	<.0001
BMI ≥26.7 kg/m^2				
Metabolic syndrome				
Yes	13.0	22.9	30.6	2.7
No	12.2	18.0	44.7	1.4
P	.57	.06	.002	.0005

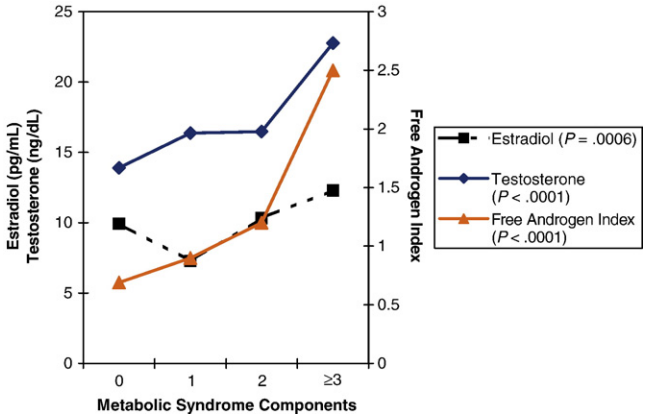

Fig. 1. Mean levels of estradiol (picograms per milliliter), testosterone (nanograms per milliliter), and FAI according to the number of metabolic syndrome components, adjusted for age and the presence or absence of CVD during follow-up.

Logistic regression models were performed to determine the odds ratio (OR) of the metabolic syndrome by tertile of endogenous sex hormone level. Tertiles were based on the distribution in women who did not meet the definition of the metabolic syndrome described above. Models were adjusted for age, smoking, physical activity, alcohol use, and presence or absence of CVD during follow-up. Because elevated BMI is strongly associated with high estrogen levels and low SHBG, as well as many components of the metabolic syndrome, analyses were repeated with additional adjustment for BMI as a continuous variable to control for confounding. Analyses were also stratified by BMI less than 26.7 kg/m^2 to evaluate potential effect modification by BMI and verify that associations were present even for women who did not have obesity by the metabolic syndrome criteria.

3. Results

Of the 212 postmenopausal women not using hormone therapy studied, 108 (51%) women had 3 or more of the metabolic abnormalities described in the modified ATP III

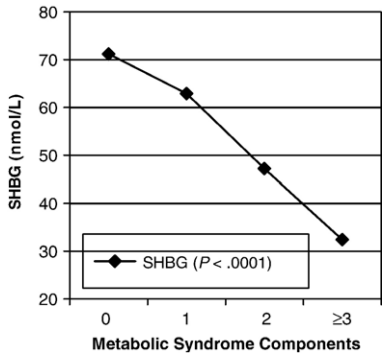

Fig. 2. Mean levels of sex hormone–binding globulin (nanomoles per liter) according to the number of metabolic syndrome components, adjusted for age and the presence or absence of CVD during follow-up.

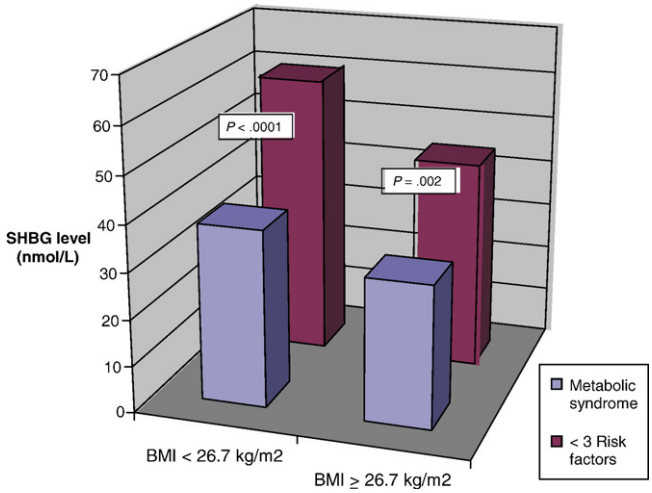

Fig. 3. Mean sex hormone–binding globulin levels (nanomoles per liter) by presence or absence of the metabolic syndrome and elevated BMI, adjusted for age and presence or absence of CVD during follow-up.

definition and, therefore, met criteria for the metabolic syndrome. Baseline characteristics of women with and without the metabolic syndrome are presented in Table 1. Women with the metabolic syndrome were slightly younger than women without the metabolic syndrome (mean age, 63.9 vs 65.8 years; $P = .03$). As expected, women with the metabolic syndrome had higher BMI (28.6 kg/m^2 compared with 23.8 kg/m^2, $P < .001$) and had more cardiovascular events during follow-up (63% compared with 37.5%, $P = .0002$). There were no other significant differences between the 2 groups in mean age of menopause, smoking, physical activity, alcohol consumption, history of oophorectomy, or parental history of MI.

Mean levels of total estradiol, total testosterone, and FAI were higher and SHBG was lower among women with the metabolic syndrome (Table 2). Low SHBG and high FAI were associated with all of the individual components of the metabolic syndrome. Higher levels of estradiol were associated with higher BMI and abnormal glucose metabolism, whereas higher levels of testosterone were found among women with low HDL level, elevated blood pressure, and elevated BMI.

There were significant trends for geometric mean levels of all sex hormones studied across increasing numbers of ATP III metabolic abnormalities, adjusted for age and the presence or absence of CVD during follow-up. As shown in Fig. 1, mean levels of estradiol ($P_{trend} = .0006$), testosterone ($P_{trend} < .0001$), and FAI ($P_{trend} < .0001$) increased according to the number of metabolic syndrome components. Lower mean levels of SHBG ($P_{trend} < .0001$) were strongly associated with increasing numbers of metabolic abnormalities (Fig. 2).

Because BMI is strongly linked to the metabolic syndrome and its components, as well as to high estradiol and low SHBG levels, the presence of obesity in many of the women with metabolic syndrome might partially explain the observed associations. We performed analyses stratified

Table 3
ORs and 95% CIs for the metabolic syndrome by tertiles of endogenous sex hormone levels

Hormone	Number with/without metabolic syndrome	Crude OR (95% CI)	Multivariate adjusted OR (95% CI)[a]	Multivariate adjusted OR + BMI (95% CI)[b]	Number with/without metabolic syndrome and BMI < 26.7 kg/m^2	Multivariate adjusted OR + BMI[b] among women with BMI <26.7 kg/m^2 (95% CI)
Estradiol[c]						
Tertile 1	16/34	Referent	Referent	Referent	8/30	Referent
Tertile 2	34/40	1.8 (0.9-3.8)	2.3 (1.0-5.3)	1.6 (0.7-3.8)	14/32	1.3 (0.4-4.1)
Tertile 3	56/29	4.1 (1.9-8.6)	4.5 (2.0-10.1)	2.0 (0.8-4.8)	5/19	0.4 (0.1-2.0)
Testosterone						
Tertile 1	19/39	Referent	Referent	Referent	8/32	Referent
Tertile 2	30/34	1.8 (0.9-3.8)	1.8 (0.8-4.0)	1.4 (0.6-3.3)	5/26	0.6 (0.1-2.3)
Tertile 3	59/31	3.9 (1.9-7.8)	4.3 (2.0-9.4)	3.2 (1.4-7.3)	14/24	1.6 (0.5-5.4)
SHBG						
Tertile 3	7/36	Referent	Referent	Referent	2/32	Referent
Tertile 2	18/34	2.7 (1.0-7.3)	2.7 (0.9-7.5)	2.5 (0.8-7.3)	7/30	3.7 (0.7-21.3)
Tertile 1	83/34	12.6 (5.1-31.0)	11.6 (4.5-29.8)	7.3 (2.7-19.8)	18/20	10.5 (2.0-56.3)
FAI						
Tertile 1	4/36	Referent	Referent	Referent	2/31	Referent
Tertile 2	18/33	4.9 (1.5-16.0)	5.9 (1.7-20.1)	4.2 (1.2-14.7)	6/28	2.4 (0.4-14.0)
Tertile 3	86/35	22.1 (7.3-66.8)	22.9 (7.3-72.1)	12.6 (3.8-41.6)	19/23	7.7 (1.4-41.4)

Tertiles were based on the distribution in women without the metabolic syndrome.
[a] Adjusted for age, smoking, physical activity, alcohol use, and the presence or absence of CVD during follow-up.
[b] Adjusted for age, smoking, physical activity, alcohol use, the presence or absence of CVD during follow-up, and BMI.
[c] There were 3 subjects missing data for estradiol.

by BMI less than 26.7 kg/m^2 (our cutpoint for abdominal obesity, which corresponded to a waist circumference of 88 cm when measured at year 6 of follow-up) to determine if relationships persisted among the leaner women (Table 2). In this subgroup, FAI and testosterone were higher and SHBG was lower among women with the metabolic syndrome. Estradiol was no longer significantly associated with the metabolic syndrome in either group. Significantly lower SHBG levels were found among women who met criteria for the metabolic syndrome, independent of BMI (Fig. 3).

To control for potential confounders, logistic regression models were performed using the metabolic syndrome as the outcome. Increased crude ORs for the metabolic syndrome were observed across tertiles of all endogenous hormones studied (Table 3). Although women with the metabolic syndrome in this study were significantly younger, adjusting for age had little effect on point estimates (data not shown). Multivariate adjustment for age, smoking, physical activity, alcohol use, and the presence or absence of CVD during follow-up showed that women in the highest tertile of estradiol had an OR for the metabolic syndrome of 4.5 (95% confidence interval [CI], 2.0-10.1) compared with women in the lowest tertile. Similarly, women in the highest tertile of testosterone had an OR of 4.3 (95% CI, 2.0-9.4). The results for SHBG and FAI were consistently stronger. Women in the lowest tertile of SHBG had an OR of 11.6 (95% CI, 4.5-29.8) for the metabolic syndrome. Among those with FAI levels in the highest compared with the lowest tertile, the OR for the metabolic syndrome was 22.9 (95% CI, 7.3-72.1).

To evaluate whether the observed associations for sex hormones and the metabolic syndrome could be explained by the known correlations with BMI, we performed analyses additionally adjusted for BMI (Table 3). The point estimates for estradiol and testosterone were attenuated, but the results for SHBG and FAI remained significant. To further limit the influence of obesity on the observed associations, we then stratified by the obesity criteria used for the metabolic syndrome (BMI <26.7 kg/m^2). Low SHBG and high FAI continued to be strongly associated with increased odds for the metabolic syndrome. Among those with SHBG levels in the lowest compared with the highest tertile, the multivariate adjusted OR (including additional adjustment for BMI) in women with BMI less than 26.7 kg/m^2 was 10.5 (95% CI, 2.0-56.3). Women with BMI less than 26.7 kg/m^2 in the highest tertile of FAI had an OR of 7.7 (95% CI, 1.4-41.4) for the metabolic syndrome.

4. Discussion

In this cross-sectional study of postmenopausal women, mean levels of estradiol, testosterone, and FAI were higher, and SHBG was lower among women with the metabolic syndrome. Low SHBG and high FAI were associated with all of the individual components of the metabolic syndrome: obesity, low HDL cholesterol level, hypertriglyceridemia, elevated blood pressure, and abnormal glucose metabolism. There were significant trends for mean levels of sex hormones and SHBG across increasing numbers of ATP III metabolic abnormalities. After multivariate adjustment, women in the highest tertile of estradiol,

testosterone, and FAI were at least 4 times more likely to have the metabolic syndrome compared with women in the lowest tertile. The OR for the metabolic syndrome among women with low SBHG was particularly strong; those in the lowest SHBG tertile were more than 10 times more likely to have metabolic syndrome compared with those in the highest SHBG tertile. The relationship between low SHBG and metabolic syndrome persisted even after adjustment for BMI.

In our prior analyses of sex hormones and CVD in postmenopausal women, those in the lowest SHBG quartile had an age-adjusted 2-fold higher risk of CVD [22]. Controlling for obesity, diabetes, hypertension, and elevated lipid levels, however, eliminated this association, suggesting that the increased cardiovascular risk attributable to low SHBG was mediated by the metabolic syndrome. The increased prevalence of the metabolic syndrome after menopause may be a direct result of ovarian failure or, alternatively, an indirect result of the metabolic consequences of central fat redistribution with estrogen deficiency [29]. There is also a higher androgen to estrogen ratio in postmenopausal than premenopausal women [30,31], which may influence the tendency to develop the metabolic syndrome.

Numerous studies have examined the relationship of endogenous sex hormones, particularly androgens, and cardiovascular risk factors in women [7-16]. The current study provides strong evidence of the relationship between low SHBG levels and the metabolic syndrome in its entirety, as well as its components, in postmenopausal women. Low SHBG levels, considered a marker of hyperandrogenism, has also been postulated to be a marker for insulin resistance [8,32], a key feature of the metabolic syndrome. An inverse association between SHBG level and both impaired glucose tolerance and diabetes was found in the Rancho Bernardo cohort [33]. Recent data from the Study of Women Across the Nation also found strong associations between low SHBG and high FAI and cardiovascular risk factors (higher insulin, glucose, and hemostatic and inflammatory markers and adverse lipids) [13].

Because SHBG is positively correlated with HDL and negatively correlated with BMI, triglyceride, and insulin levels, it has been suggested that low SHBG level should be one of the components of the metabolic syndrome in women [34]. Few studies, however, have investigated endogenous sex hormones and the clustering of cardiovascular risk factors in women. Premenopausal women with the metabolic syndrome were found to have lower SHBG levels and higher FAI than age-matched controls; no significant difference in total testosterone was observed [17]. A recent community-based study of postmenopausal women also found associations between FAI, but not total testosterone, and the metabolic syndrome (SHBG was not reported separately) [18]. Although it has been reported that high SHBG levels confer risk reduction for the metabolic syndrome in men and premenopausal women, a significant relationship was not found in postmenopausal women [19]. Our findings may differ because of the high-risk population studied, and, therefore, the increased number of women who met criteria for the metabolic syndrome. Furthermore, this high-risk population may have been particularly suited to demonstrate the association between low SHBG and the metabolic syndrome, given that we used BMI to define the cutpoint for obesity and that almost half of participants exceeded this cutpoint.

Because the complex biological mechanisms that explain the association between low SHBG and the metabolic syndrome are not fully understood, it is unknown whether low SHBG levels are deleterious per se or are simply a marker of metabolic derangement. Total and central obesity are inversely related to SHBG in women [35,36], and both adipokines and insulin may be direct and indirect negative regulators of SHBG secretion by the liver. SHBG has been hypothesized to affect atherogenesis both directly and indirectly through lipoprotein metabolism or affecting the equilibrium of the estradiol-testosterone balance [37]. Testosterone has a higher affinity than estradiol for SHBG, so a small decrease in SHBG results in a relatively more androgenic hormone profile. SHBG levels may also be affected by other metabolic parameters such as elevated local cortisol production in abdominal adipose tissue and/or nutritional factors [19].

Although adiposity may be one mediator of the observed relationships, we did not adjust for BMI in the primary analysis because the presence of abdominal obesity is part of the definition and underlying physiology of the metabolic syndrome. To determine, however, whether BMI alone explains these strong associations, additional analyses controlling for BMI were performed. Analyses were also stratified by our cutpoint for obesity (BMI <26.7 kg/m^2). The association of low SHBG and high FAI with the metabolic syndrome remained strong, suggesting that the relationships between low SHBG and high FAI and the metabolic syndrome are relatively independent of obesity. Although these analyses investigated the confounding role of BMI, rather than waist circumference, BMI is a more frequent measure of adiposity in the clinical setting.

The percentage of women in our study with the metabolic syndrome (51%) was somewhat higher than in other published cohorts because our population was enriched with women who were selected for a prior case-control study based on their development of CVD during follow-up. In the National Health and Nutrition Survey, 43.5% of women aged 60 through 69 years had the metabolic syndrome [20]. Although the high-risk women in this study may not be completely representative of the general population, it is likely that the underlying biologic associations between endogenous hormones and metabolic abnormalities will be similar in other postmenopausal women.

This analysis has several limitations. Hormone measurements were available only at baseline, thereby restricting us to cross-sectional analyses. Therefore, neither causality nor

the temporality of the association can be proven. Although only one measure of hormones was available, levels are relatively stable in postmenopausal women [38]. Because only estradiol, testosterone, and SHBG were measured, we were unable to investigate whether additional endogenous sex hormones were also associated with the metabolic syndrome. Although we lacked direct measurements of waist circumference, weight, blood pressure, and fasting blood glucose at baseline, this modified definition of the metabolic syndrome was used previously in this cohort and was predictive of CVD in a prior study [25].

The use of direct RIA testosterone assays in women, who usually have testosterone concentrations below the lower limit of the normal adult male range, has been challenged [39,40]. Free levels of testosterone were not available; however, a recent comparison of methods showed that direct free testosterone RIA measurements had unacceptably high systematic bias and random variability [41]. Calculated FAI is highly correlated with free testosterone [23,24,41], although its accuracy depends on the testosterone and SHBG assays. Rather than absolute accuracy, however, the validity of these positive associations depends on the precision of the assays. A frameshift bias would not affect relationships because the relative ranking of subjects would be similar. Random measurement error would tend to diminish the strength of associations; therefore, the especially strong association between SHBG and the metabolic syndrome remains compelling. Additional studies will be warranted using improved testosterone, free testosterone, and SHBG assays, as they become available.

In summary, we found that levels of endogenous sex hormones were associated with the metabolic syndrome and its individual components. Women with low SHBG levels and high FAI values had a dramatically higher prevalence of metabolic syndrome. The metabolic syndrome was less strongly associated with increased levels of testosterone and estradiol. The association with estradiol was not present among leaner women, suggesting that this association was mediated primarily by obesity. Hyperandrogenism has been previously associated with the metabolic syndrome [42] and its individual components [43] in premenopausal women with polycystic ovarian syndrome. The current study extends these observations to postmenopausal women, the population with the greatest risk of cardiovascular morbidity and mortality from the metabolic syndrome.

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