SHBG levels correlate with insulin resistance in postmenopausal women

Fulya Akin,⁎ Mehmet Bastemir, Esma Alkış, Bunyamin Kaptanoglu

Pamukkale University Faculty of Medicine Department of Endocrinology and Metabolism, Denizli, 20070, Turkey
Pamukkale University Faculty of Medicine Department of Public Health, Turkey
Pamukkale University Faculty of Medicine Department of Biochemistry, Turkey

Received 16 February 2007; received in revised form 26 August 2007; accepted 27 September 2007
Available online 30 July 2008

Abstract

Background: Overweight or central obesity is generally associated with increases in fasting insulin levels, insulin resistance, and glucose intolerance and has been identified as a target for new therapeutic strategies, including early change in lifestyle. Early biochemical markers for identifying at-risk patients will be useful for prevention studies. The aim of this study is to investigate whether or not SHBG level is a useful index of hyperinsulinemia and/or insulin resistance in pre- and postmenopausal obese women. At the same time, the relationship between SHBG concentrations and features of the metabolic syndrome were evaluated.

Methods: 229 women were eligible for this study. MetS was defined by using a modification of the ATP III guidelines. All patients were euthyroid, obese and overweight, 25 to 69 years of age. Subjects were divided into groups of premenopausal women (n=125) and postmenopausal women (n=104). Various fatness and fat distribution parameters, SHBG, sex hormones, FSH, LH, thyroid hormones, serum levels of fasting and postprandial glucose, lipid profile, uric acid and serum insulin, and blood pressure were measured.

Results: No significant difference was found in mean SHBG levels between pre- and postmenopausal obese women in this study (p=0.866).

In premenopausal obese women, SHBG correlated negatively with BMI, waist circumference, fasting glucose, uric acid levels and FAI.

In postmenopausal obese women, SHBG correlated negatively with fasting glucose, postprandial plasma glucose, fasting insulin, HOMA-IR and FAI and positively with HDL.

SHBG had a significant inverse association with MetS parameters only in postmenopausal women, also after adjusting for BMI, age and estradiol.

Conclusions: Obesity may influence the levels of endogenous sex steroid, especially after menopause. SHBG concentrations are correlated with features of the metabolic syndrome, particularly in postmenopausal obese women.

These results suggest that SHBG may be an index of insulin resistance in postmenopausal obese women.

© 2008 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.

Keywords: Sex hormone binding globulin; Obesity; Metabolic syndrome; Insulin resistance; Sex hormones

1. Introduction

Metabolic syndrome (MetS), is a precursor state for cardiovascular disease. Overweight or central obesity is generally associated with increases in fasting insulin levels, insulin resistance and glucose intolerance, and has been identified as a target for new therapeutic strategies, including early change in lifestyle. Early biochemical markers for identifying at-risk patients will be useful for prevention studies. The main goal of the present study was to search for such tools.

Sex hormone binding globulin (SHBG) is the main transport protein for testosterone and estradiol and modulates their biological activity. It is mainly synthesized in the liver [1–3] and binds testosterone with high affinity and estrogens with lower affinity. The SHBG together with IGF-binding protein-1 is down-regulated by insulin. Therefore, it is known that they could serve as potential indicators of the MetS and hyperinsulinemia-related cardiovascular risk [4]. At present there is also a recent and excellent systematic review and meta-analysis
published in JAMA that indicates that endogenous sex hormones may differentially modulate glycemic status and risk of type 2 diabetes in men and women [5]. Endogenous levels of testosterone and SHBG each exhibit sex-dependent relations with risk of type 2 diabetes, such that the inverse association of SHBG was stronger in women than in men [5]. Association between low SHBG and the development of type 2 diabetes has also been reported in both sexes, although most works have been developed in males [4,6–10]. In women, being overweight and insulin resistant are frequently associated with the presence of clinical symptoms of hyperandrogenemia as well as with elevated serum levels of testosterone and low serum levels of SHBG [11–15]. The finding of low serum levels of SHBG is suggested to be a strong predictor of the subsequent development of diabetes in pre- and postmenopausal women [9]. Low SHBG frequently coincides with components of MetS, such as low levels of HDL cholesterol and high levels of triglycerides and apolipoprotein B [16–19].

In this study, SHBG concentrations were determined in premenopausal and postmenopausal obese women and the relationship between SHBG concentrations and features of the metabolic syndrome was evaluated.

2. Materials and methods

2.1. Subjects

This cross-sectional analysis was carried out on 350 obese and overweight patients aged 25 to 69 years referred to the Department of Endocrinology and Metabolic Diseases of Pamukkale University Hospital in 2002–2003.

All of the patients were obese and overweight, BMI > 25 kg/m². Patients who were under treatment with contraceptive drugs or hormone replacement therapy (HRT) or who were diagnosed with polycystic ovary syndrome, thyroid disease, chronic renal failure, chronic hepatopathy or cancer, were excluded from the study. Patients who had been diagnosed as DM previously were also excluded. The patients who were diagnosed as DM during the study were not excluded. The patients who were taking any medication known to interfere with glucose or insulin secretion and/or metabolism (e.g., metformine and other oral antidiabetics) were also excluded from the analyses. Patients taking antihypertensive drugs and statins were also excluded. The presence of medical conditions was assessed through self-report. Thyroid status was assessed by freeT3 (fT3), freeT4 (fT4), and thyrotropin (TSH) levels.

Insulin resistance was estimated by homeostatic model assessment ratio formula [20].

\[
\text{HOMA-IR} = \frac{(\text{Fasting plasma insulin} \times \text{Fasting plasma glucose})}{22.5}
\]

Free androgen index (FAI) was used to estimate the amount of testosterone unbound by SHBG and thus, immediately biologically active.

FAI was calculated as the ratio testosterone (ng/ml)/SHBG (ng/ml) × 100 [21].

229 women were eligible for this study. Patients were divided into groups of premenopausal women (n=125) and postmenopausal women (n=104).

The definition of menopausal status was in accordance with the following criteria [22]:

Women in amenorrhea for at least 12 months, having follicle stimulating hormone levels higher than 12.75 IU/l, were included in the postmenopausal group.

Women presenting normal menses or who in any case reported at least 10 cycles in the previous year and without climacteric-related symptoms, and having follicle stimulating hormone levels lower than 12.75 IU/l, were included in the premenopausal group.

2.2. Anthropometric measurements

Height and weight were measured in light clothing without shoes. Body height was measured by a statorimeter and body weight by digital electronic weighing scale. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Waist circumferences were measured using a flexible measuring tape, midway between the xiphoid and the umbilicus during the midinspiratory phase.

Anthropometric measurements were carried out three times by a single tester.

Body water and fat distribution was assessed by multiple frequency bioelectric impedance measurement with a portable impedance analyzer (Tanita, Tokyo, Japan).

2.3. Blood pressure

The average of two measurements of blood pressure (BP) with the subject in the sitting position was taken at a 2 to 3 min interval after resting for at least 15 min.

2.4. Metabolic syndrome definition

The metabolic syndrome (MetS) was defined by an NIH Expert Panel (referred to as the ATPIII guidelines) [23]. MetS was defined as the presence of three or more of the following (values in parentheses are for women):

1. Waist circumference (cm) > 102 (>88)
2. Systolic BP > 130 mm Hg or diastolic BP > 85 mm Hg
3. HDL cholesterol < 40 (<50) mg/dl
4. Impaired fasting glucose (IFG), fasting plasma glucose > 110 mg/dl
5. Triglycerides > 150 mg/dl.

2.5. Laboratory analyses

Serum levels of fasting and postprandial glucose, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol and uric acid were analyzed with commercial kits (Beckman – Coulter, USA) in an autoanalyzer (Beckman – Coulter LX-20, USA), while the levels of serum insulin, fT3, fT4, TSH, testosterone,
Correlation is significant at the 0.01 level (2-tailed). Results are expressed as means±SD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Premenopausal women (n=125)</th>
<th>Postmenopausal women (n=104)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages (years)</td>
<td>35.62±9.27</td>
<td>50.83±7.79</td>
<td>0.000*</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88.96±16.11</td>
<td>88.05±15.32</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.44±5.05</td>
<td>155.77±6.08</td>
<td>0.000*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>35.39±6.07</td>
<td>36.25±5.78</td>
<td>NS</td>
</tr>
<tr>
<td>Waist circumferences (cm)</td>
<td>95.45±11.94</td>
<td>96.87±10.14</td>
<td>NS</td>
</tr>
<tr>
<td>Fat % (Tanita)</td>
<td>41.95±7.98</td>
<td>43.65±5.75</td>
<td>NS</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>45.28±34.68</td>
<td>46.09±31.99</td>
<td>0.866</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>121.19±16.41</td>
<td>130.55±20.08</td>
<td>0.000**</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>79.71±9.90</td>
<td>84.54±10.59</td>
<td>0.001**</td>
</tr>
<tr>
<td>Fasting insulin (µIU/ml)</td>
<td>114.85±44.25</td>
<td>122.44±43.17</td>
<td>0.214</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>13.18±5.84</td>
<td>10.56±4.82</td>
<td>0.001**</td>
</tr>
<tr>
<td>TSH (µIU/ml)</td>
<td>3.41±1.83</td>
<td>2.92±1.77</td>
<td>0.056</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>118.00±34.68</td>
<td>207.00±32.29</td>
<td>0.000**</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>45.61±11.55</td>
<td>51.12±13.07</td>
<td>0.001**</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>6.45±2.96</td>
<td>55.14±31.53</td>
<td>0.000**</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>5.84±8.44</td>
<td>23.75±15.37</td>
<td>0.000**</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>112.79±95.12</td>
<td>56.10±42.90</td>
<td>0.000**</td>
</tr>
<tr>
<td>Total testosterone (ng/dl)</td>
<td>46.66±11.23</td>
<td>46.7±12.26</td>
<td>0.965</td>
</tr>
<tr>
<td>Free androgen index (FAI)</td>
<td>2.41±3.39</td>
<td>1.60±1.47</td>
<td>0.052</td>
</tr>
<tr>
<td>DHEAS</td>
<td>169.34±87.29</td>
<td>113.56±76.66</td>
<td>0.000**</td>
</tr>
</tbody>
</table>

Results are expressed as means±SD.
* Difference is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

estradiol (E2), sex hormone binding protein, FSH and LH were determined in an immunanalyzer (Immulaite 2000, USA) using the chemiluminescence method. Intra-assay coefficients of variations (CV) for SHBG and total testosterone assays were 2.7% and 13.0% respectively. Inter-assay CV were 5.2% and 16.4%. For SHBG, the lower limit of detection was 0.02 nmol/l.

2.6. Statistical analyses

Descriptive statistics, proportions for categorical variables and means and standard deviations for continuous variable, were used to describe the study groups. Comparisons between premenopausal and postmenopausal women groups were analyzed with Student’s t test. Correlations between SHBG levels and MetS parameters were evaluated by Pearson’s correlation coefficient and with linear regression analyses. The multivariant regression analysis was performed by using the Backward method. Partial correlations adjusting for age; age and body mass index (BMI); age, BMI and sex steroids were computed to assess associations between plasma concentrations of SHBG and MetS parameters. All statistical analyses were performed using SPSS 9.0 software (SPSS Inc.).

3. Results

The patient characteristics (means and SD) of the studied groups are shown in Table 1.

Pre- and postmenopausal women had similar BMI, waist circumference and fat % (Tanita).

No significant difference was found in mean SHBG levels between pre- and postmenopausal women in this study (p=0.866).

Postmenopausal women had higher systolic and diastolic blood pressure, fasting glucose, and total cholesterol, LDL cholesterol, and HDL cholesterol levels. Premenopausal women had higher fasting insulin and DHEAS. Also, it has been seen that FAI was slightly lower in postmenopausal women than in premenopausal women, but the difference was not statistically significant (p=0.052).

Table 2

<table>
<thead>
<tr>
<th>Variables</th>
<th>SHBG (nmol/l)</th>
<th>Total testosterone (ng/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Premenopausal</td>
<td>Postmenopausal</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>−0.201*</td>
<td>−0.083</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>−0.0205*</td>
<td>0.025</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>0.019</td>
<td>−0.016</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>−0.011</td>
<td>−0.010</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>−0.204*</td>
<td>−0.010</td>
</tr>
<tr>
<td>2 h postprandial glucose (mg/dl)</td>
<td>−0.162</td>
<td>0.239*</td>
</tr>
<tr>
<td>Fasting insulin (µIU/ml)</td>
<td>−0.101</td>
<td>−0.072</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>−0.170</td>
<td>−0.049</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>0.141</td>
<td>0.030</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>0.252*</td>
<td>0.029</td>
</tr>
<tr>
<td>Total testosterone (ng/dl)</td>
<td>−0.083</td>
<td>−0.083</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>−0.044</td>
<td>−0.124</td>
</tr>
<tr>
<td>DHEAS</td>
<td>−0.143</td>
<td>0.290**</td>
</tr>
<tr>
<td>Fat (Tanita)</td>
<td>−0.009</td>
<td>0.009</td>
</tr>
<tr>
<td>Free androgen index (FAI)</td>
<td>−0.283**</td>
<td>0.927**</td>
</tr>
</tbody>
</table>

Results are reported as pearson’s rank value correlation coefficient (r-value).
*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).
NS, Non significant.
In premenopausal obese women, SHBG correlated negatively with BMI, waist circumference, fasting glucose, uric acid levels and FAI. Linear regression analysis (Backward) also showed that uric acid and FAI were independent determinants of SHBG in premenopausal women (regression summary, $r = 0.379$, $R^2 = 0.143$ ($p = 0.043$, $p = 0.024$, respectively) (Fig. 1).

In postmenopausal obese women, SHBG correlated negatively with fasting glucose, postprandial plasma glucose, fasting insulin and HOMA-IR and positively with HDL. In this group, using linear regression analysis (Backward), FAI and HDL were selected as predictor variables for SHBG (regression summary, $r = 0.536$, $R^2 = 0.287$; $p = 0.000$, $p = 0.007$, respectively) (Fig. 2). Table 2 summarizes Pearson’s correlation coefficients between SHBG and testosterone and MetS parameters.

In premenopausal women, SHBG correlated with BMI, waist circumference and uric acid after adjusting for age. However, none of the associations remained significant after adjusting for age, BMI and estradiol.

In age-adjusted analysis, the association between low SHBG and insulin resistance (HOMA % sensitivity) remained significant in postmenopausal women. SHBG had a significant inverse association with MetS parameters only in postmenopausal women, also after adjusting for BMI, age and estradiol.

4. Discussion

In this study, SHBG concentrations were determined in pre- and postmenopausal obese women and the relationships between SHBG concentrations and features of the metabolic syndrome were evaluated.

Interestingly, this study shows strong relationships between SHBG and anthropometric measurements and indices of insulin resistance in postmenopausal women but not in premenopausal women.

In women, menopause-induced estrogen deficiency and increased androgenicity are associated with increased abdominal obesity and with the concomitant alterations in the metabolic risk profile [24]. In this study, we found that total or intra-abdominal obesity mediated an important part of the relation between low SHBG and an altered metabolic profile by using BMI and waist circumference. The results of the present study are concordant with previous investigators [25–27]. Furthermore, a recent prospective study identified low levels of SHBG as a risk factor for future diabetes mellitus [28].

SHBG levels decrease with increasing waist circumference, particularly in the postmenopausal group. In our group of postmenopausal women, insulin resistance and HOMA index were strongly associated with SHBG levels, suggesting that the severity of insulin resistance is a determinant factor in SHBG level. Our results are in agreement with a recent study by Reinecke et al. [29] who reported that SHBG is a more sensitive marker of the pathogenetic contribution of insulin resistance to the pathogenesis of atherosclerosis than insulin itself.

Most cross-sectional studies have reported that SHBG and testosterone levels correlate positively with HDL cholesterol levels between sexes [17]. Our study shows that in postmenopausal women, SHBG correlated positively with HDL cholesterol. In this group, FAI and HDL were selected as predictor variables for SHBG (as shown in Fig. 2). Testosterone correlated positively with waist circumference and HDL cholesterol too. Also, in postmenopausal women, testosterone correlated with postprandial glucose levels, which is an important cardiovascular disease risk.

Determinants of SHBG blood concentrations are likely to change with the passing from premenopausal to postmenopausal status [30]. Pasquali et al. showed that in the premenopausal group, SHBG levels were correlated positively with estradiol and negatively with testosterone and insulin, but not with the WHR. On the contrary, in the postmenopausal group, SHBG values had a significant negative correlation with the WHR, whereas the relationship with estradiol was not significant; moreover, the relationship with testosterone and insulin, although significant, became less marked. This study indicated that SHBG values are correlated positively with estradiol and negatively with insulin and testosterone concentrations, but the predictive value of these variables on SHBG appears to be different in premenopause and...
postmenopause, and SHBG levels decrease with increasing WHRs, particularly in the postmenopausal group. Since abdominal body fat distribution is associated with both hyperinsulinemia and increased free testosterone fraction, it is possible that the negative correlation between WHR and SHBG may be primarily mediated by these factors [30]. It is well-known that estrogens increase the synthesis and blood levels of SHBG. After menopause, estrogen concentrations are directly related to the amount of adipose tissue; increased BMI may lead to an enhanced ovarian synthesis of androgens. A large amount of data have demonstrated that insulin can be an important inhibiting factor of SHBG synthesis [31]. Numerous epidemiologic studies have in fact demonstrated a significantly negative correlation between insulin concentrations and SHBG blood levels, suggesting a cause-and-effect relationship [32]. The effect of BMI appears to be stronger for postmenopausal than premenopausal status. Therefore, it could be argued that SHBG level can be correlated with insulin resistance for the postmenopausal women. We found significant reduction of mean fasting insulin blood levels after menopause (see Table 1). It is known that estrogens protect pancreatic β-cells from apoptosis and have insulinotropic effects [33]. In postmenopausal status this effect is lost and insulin levels decrease. Our results also confirm this. The positive effect of estradiol on SHBG levels is probably stronger in premenopausal women than in postmenopausal women. It has been noted that after the menopause, the impact of insulin resistance on SHBG level seems more important than estradiol (unpublished data).

That is why SHBG correlated with insulin resistance and MetS component in only postmenopausal women.

The accelerated accretion of adipose tissue in the intra-abdominal region coincident with the onset of menopause may explain part of the increased risk of cardiovascular disease in postmenopausal women [29]. Our results confirm this association. In a longitudinal study by Poehlman et al. [34], women who experienced menopause had a greater increase in fat mass and waist-to-hip ratio compared with women who remained premenopausal. Increases in central body adiposity have been found to be associated with adverse metabolic consequences, including insulin resistance and hypertriglyceridemia [35]. The women with lower SHBG values (indicating greater androgenicity) were found to have an increased incidence of diabetes mellitus.

Lee et al. [36] reported that there is a significant association between insulin sensitivity and androgenicity in postmenopausal women that is independent of obesity and central adiposity. They concluded that, in addition to weight loss, interventions to decrease androgenicity may therefore be useful in improving insulin sensitivity in postmenopausal women.

In contrast to the results in postmenopausal women, we did not find any correlation between SHBG concentrations and insulin resistance in premenopausal women. According to our findings, low plasma SHBG levels were associated with an altered metabolic profile in premenopausal women. Low SHBG concentrations may indicate visceral obesity and glucose intolerance in premenopausal women. Similar findings were reported by Cikim et al. [26], who aimed to evaluate the relationship between SHBG concentrations and features of the MetS in premenopausal healthy obese women. Their low SHBG group was significantly younger, with higher waist-to-hip ratio (WHR). Triglycerides, uric acid, insulin and HOMA values were significantly lower in their low SHBG group. They reported that low SHBG concentrations may indicate a severe degree of insulin resistance in premenopausal women.

Decreased SHBG has been shown to be predictive of the incidence of metabolic syndrome in women, and of subsequent development of cardiovascular disease and overall mortality in postmenopausal women. SHBG is an index of insulin resistance and might be useful in epidemiological studies of cardiovascular risk in women. Our findings also confirm these results. In postmenopausal women, the SHBG decrease is consistently related to the increase in insulin. These results suggest that SHBG is a good marker for hyperinsulinism in postmenopausal women. The cause-and-effect relationships between SHBG concentrations and MetS components in obese women could not be assessed because of the cross-sectional nature of our study.

It is concluded that low SHBG concentrations may indicate visceral obesity and glucose intolerance in premenopausal women. Although insulin is still the most convenient marker, we have shown that SHBG might be a surrogate marker for insulin resistance in postmenopausal overweight women.

5. Learning point

- SHBG may play a role as a marker for insulin resistance in postmenopausal overweight women.

References


