The Impact of Obesity on Hormonal Parameters in Hirsute and Nonhirsute Women

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The influence of obesity on sex hormone–binding globulin (SHBG) and androgen concentrations in hirsute and nonhirsute women has been evaluated. The study was performed in 226 hirsute women (88 obese and 138 non-obese) classified as being affected by polycystic ovarian syndrome (PCOS) or by idiopathic hirsutism (IH) and in 100 nonhirsute control women ([C] 60 lean and 40 obese). SHBG, free testosterone (fT), androstenedione (A), estradiol (E2), dehydroepiandrosterone sulfate (DHEAS), and gonadotropin levels were measured during the first week of the menstrual cycle by radioimmunoassay (RIA). A significant negative correlation between SHBG and body mass index (BMI) was observed in PCOS, IH, and C women. In obese women—whether PCOS, IH, or C—fT levels were significantly higher and, conversely, SHBG levels were lower than in non-obese women. A negative correlation between SHBG and fT was evidenced in each group. Upper-body obesity was associated with lower SHBG and higher fT levels than lower-body obesity. In conclusion, obesity, particularly upper-body obesity, is associated with a reduction in SHBG and an increase in fT in both nonhirsute and hirsute women.

OBESITY influences many endocrine functions, inducing alterations in sex hormone metabolism in men and women. Several studies on obese subjects have reported an increase in androgen production rate, in peripheral conversion of androgens to estrogens, and in estrogen production rate.[1,2] Furthermore, obesity is associated with a decrease in sex hormone–binding globulin (SHBG), and consequently with an increase in free-hormone levels and in the metabolic clearance rate of several steroid hormones.[2] Moreover, obesity in women is frequently associated with menstrual disturbances and with a higher risk of androgenic ovulatory dysfunction.[3,4] Indeed, obesity, hirsutism, and sterility are the most frequent symptoms of polycystic ovarian syndrome (PCOS), and obesity may play some role in the pathophysiology of this syndrome.[4-7] In patients with PCOS, serum SHBG concentrations are lower in obese than in lean women and, conversely, free-testosterone (fT) levels are higher.[4,5,8] In hirsute women, a variable reduction in SHBG has been shown, and SHBG levels have been correlated with body weight rather than with androgen concentrations.[9,10] In premenopausal normal women, it is reported that SHBG level is related to adiposity, whereas a significant correlation between SHBG and androgen concentrations has not always been demonstrated.[4,5,10-13] However, not all obese women have reduced SHBG levels. This suggests that other factors could be involved in the regulation of SHBG synthesis or metabolism, eg, estrogens, thyroid hormones, nutritional factors, and insulin.[4,5,14,15]

Differences in body fat distribution have also been related to differing sex hormone concentrations in obesity. Evans et al[11] noted that body mass index (BMI) and waist to hip ratio (WHR) correlated inversely with SHBG levels and directly with the proportion of fT. In that study, upper-body obesity was associated with greater endocrine and metabolic complications than lower-body obesity. An increased WHR may be an epiphenomenon of hyperinsulinemia, but its relation to androgen is unclear.[16]

The aim of our study was to evaluate possible differences in fT, androstenedione (A), dehydroepiandrosterone sulfate (DHEAS), estradiol (E2), and serum SHBG concentrations between obese and non-obese hirsute and nonhirsute women, to better define the impact of obesity on these endocrine parameters.

SUBJECTS AND METHODS

Subjects

Study subjects were 226 hirsute women who presented consecutively to our division. A modification of the Ferriman-Gallwey score was used to evaluate the degree of hirsutism, taking into consideration hair distribution in eight areas (upper lip, cheeks, chin, chest, upper and lower abdomen, and upper and lower back).[17] The severity of hirsutism in each of these areas was graded from 1 (least severe) to 4 (most severe), with a maximum score of 32.

No evidence of ovarian or adrenal neoplasm, prolactinoma, Cushing's syndrome, congenital adrenal hyperplasia, or drug-induced hirsutism was found. All women were euthyroid as assessed by normal serum free thyroxine, free triiodothyronine, and thyrotropin levels. They had not undergone any medical therapy for hirsutism for at least 3 months before the study.

Blood samples were taken between 8 and 9 AM for hormonal evaluation during the first week of the menstrual cycle (spontaneous or progestin-induced in amenorrheic patients).

Eighty-eight patients aged 16 to 40 years were obese (BMI > 25 kg/m^2), and 135 aged 17 to 40 years were not obese (BMI 18 to 25 kg/m^2). Sixty non-obese women (mean age, 22.5 ± 5.3 years) and 52 obese women (mean age, 23.2 ± 6.9) were diagnosed as having PCOS on the basis of hyperandrogenism with elevated testosterone level and/or luteinizing hormone (LH) to follicle-stimulating hormone (FSH) ratio, anovulatory cycles, and the presence of polycystic ovaries (> 10 follicles and enlarged ovaries) on ultrasonography.

Seventy-eight non-obese patients (mean age, 23.2 ± 5.4 years) and 36 obese patients (mean age, 24.7 ± 6.6) had hirsutism in the absence of any known underlying disease. These patients had regular ovulatory cycles as assessed by progesterone determination

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Table 1. Hormonal Concentrations in PCOS, IH, and C Women

Hormone	PCOs (n = 112)	IH (n = 114)	C (n = 100)
LH (mIU/mL)	4.5 ± 3.0	2.8 ± 1.3	3.0 ± 1.7
FSH (mIU/mL)	4.4 ± 2.1	4.8 ± 2.2	5.4 ± 3.0
E2 (pg/mL)	39.0 ± 24.3	36.9 ± 22.4	43.1 ± 32.9
fT (pg/mL)	3.7 ± 1.2	1.9 ± 0.7	1.6 ± 0.7
SHBG (nmol/L)	44.0 ± 26.7	60.0 ± 26.1	63.3 ± 25.7
A (ng/mL)	2.6 ± 0.9	1.7 ± 0.8	1.5 ± 0.7
DHEAS (μg/mL)	2.6 ± 0.9	2.3 ± 0.8	2.0 ± 0.9

on the 24th day of the cycle, and were classified as having idiopathic hirsutism (IH).

Sixty lean and 40 obese nonhirsute, eumenorrheic, age-matched (16 to 40 years) women studied in the same phase of the menstrual cycle served as controls (C). None of these women had a history of endocrinopathies or presented with thyroid, renal, or hepatic abnormalities.

Hormonal Assay

Sera were analyzed for LH, FSH, prolactin, E2, and progesterone using commercially available radioimmunoassay (RIA) kits (Serono, Rome, Italy). fT and DHEAS levels were measured by means of a solid-phase RIA (Diagnostic Products, Los Angeles, CA). Intraassay coefficients of variation (CVs) for the measurement of fT and DHEAS were 7%, 6%, and 5% for low, medium, and high values, respectively. A level was measured, after sample extraction, by means of coated-tube RIA (Diagnostic Products) with CVs of 10%, 5%, and 6%, respectively. SHBG levels were determined by a solid-phase immunoradiometric assay (Diagnostic Products) with a CV of 3%. In all assays, interassay CVs were 5% to 10%. In our laboratory, androgen levels at the upper 95th percentile in normal women were as follows: fT, less than 2.7 pg/mL; A, less than 3.2 ng/mL; DHEAS, less than 3.6 μg/mL; and SHBG, less than 80 nmol/L (follicular phase).

Statistical Analysis

Results are expressed as the mean ± SD unless otherwise indicated. Statistical analysis was performed using Student's *t* test; *P* less than .05 was considered significant. Linear regression analysis was used to analyze possible correlations between endocrine findings.

RESULTS

When considering the study population according to diagnosis, the PCOS group exhibited significantly higher fT ($P < .001$), A ($P < .001$), and LH ($P < .01$) levels than IH and C groups. IH patients also exhibited higher fT and A levels than C subjects ($P < .05$). Mean SHBG concentrations were lower in PCOS subjects than in either IH or C women ($P < .01$; Table 1). When the study groups were examined according to BMI, 46% of PCOS, 31.5% of IH, and 40% of C subjects were classified as obese. The mean age did not differ between obese and non-obese subjects. In obese women—whether PCOS, IH, or C—plasma fT levels were significantly higher ($P < .01$) than in non-obese women; conversely, SHBG was lower ($P < .001$). A, DHEAS, E2, and LH concentrations were not significantly different in obese and non-obese women within each group (Table 2).

A significant negative correlation ($P < .0001$) between SHBG and BMI was observed in PCOS (Fig 1), IH ($r = -.43$), and C women ($r = -.47$). fT also correlated with SHBG (PCOS, $r = -.32$; IH, $r = -.44$; C, $r = -.41$; $P < .001$) and with BMI (PCOS, $r = .39$; IH, $r = .34$; C, $r = .39$; $P < .001$).

In obese subjects, a negative correlation between SHBG and fT concentrations was found within each group (PCOS, $r = -.38$; IH, $r = -.46$; C, $r = -.50$; $P < .01$). A significant correlation was observed between BMI and SHBG levels in C women and in IH obese women (C, $r = -.38$; IH, $r = -.41$; $P < .01$), whereas in obese PCOS patients, such a correlation did not reach statistical significance ($r = -.28$). A positive correlation was also seen between BMI and fT in obese controls, although at a lower level of significance ($r = .33$, $P < .05$).

Since measurement of body circumferences (WHR) can provide a reliable estimate of body fat distribution,[5] obese patients were further classified as having upper-body (WHR > 0.85) or lower-body (WHR ≤ 0.75) obesity. Upper-body obesity was found in 32 of 52 PCOS (61.5%), 16 of 36 IH (44.4%), and 21 of 40 C (52.5%) women. Lower-body obesity was found in 11 PCOS (21.1%), 11 IH (30.5%), and 12 C (30%) subjects. The remaining women had WHR between 0.76 and 0.85.

Serum hormone concentrations were compared in the two obesity phenotypes and are presented in Table 3. A significant difference in fT ($P < .001$) and SHBG levels ($P < .05$) was found in C women with upper-body obesity as compared with women with lower-body obesity. Similarly, fT levels were higher ($P < .005$) and, conversely, SHBG concentrations were lower in upper-body than in lower-body obese IH subjects. No significant differences were found in fT and SHBG concentrations between android or gynoid obese PCOS patients. Serum E2, DHEAS,

Table 2. Hormonal Concentrations and BMI in Non-obese and Obese PCOS, IH, and C Women

	PCOS		IH		C	
Hormone	Non-obese	Obese	Non-obese	Obese	Non-obese	Obese
LH (mIU/mL)	4.7 ± 3.0	4.3 ± 2.9	3.0 ± 1.5	2.5 ± 0.8	3.1 ± 1.9	2.9 ± 1.3
FSH (mIU/mL)	4.2 ± 2.1	4.3 ± 2.2	5.0 ± 2.2	4.5 ± 2.1	5.6 ± 3.2	5.2 ± 2.8
E2 (pg/mL)	42.7 ± 24.4	34.7 ± 23.6	35.9 ± 19.4	39.0 ± 27.8	44.0 ± 29.4	41.2 ± 38.0
fT (pg/mL)	3.3 ± 1.1	4.1 ± 1.3	1.7 ± 0.6	2.3 ± 0.7	1.4 ± 0.6	1.9 ± 0.9
SHBG (nmol/L)	55.3 ± 28.6	31.5 ± 17.5	67.2 ± 26.3	44.2 ± 17.3	73.8 ± 23.7	49.8 ± 23.5
A (ng/mL)	2.6 ± 0.9	2.7 ± 0.9	1.6 ± 0.7	1.9 ± 1.0	1.5 ± 0.6	1.5 ± 0.7
DHEAS (μg/mL)	2.6 ± 1.0	2.5 ± 0.8	2.3 ± 0.9	2.3 ± 0.7	1.9 ± 0.8	2.1 ± 1.1
BMI (kg/m^2)	20.9 ± 1.9	31.5 ± 3.6	21.3 ± 2.7	30.0 ± 4.3	21.3 ± 2.0	31.8 ± 7.2

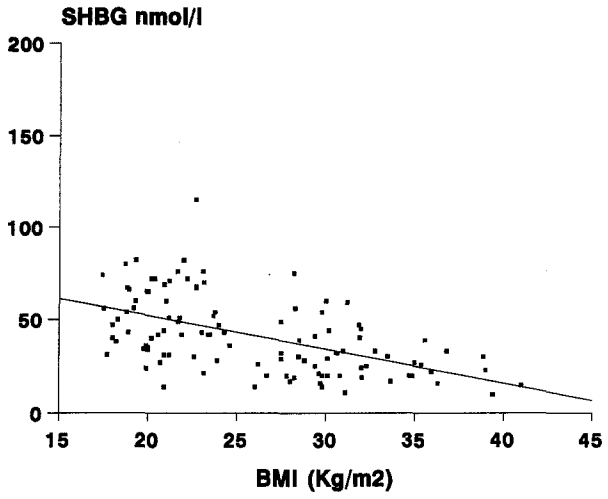

Fig 1. Inverse relationship between BMI and SHBG levels in PCOS hirsute women; $r = -0.49$, $P < .0001$.

FSH, and LH were similar in both subgroups, whereas A levels were higher in upper-body obese C and IH women. In subjects with a WHR between 0.76 and 0.85, fT and SHBG concentrations were similar to those in upper-body obese women (data not shown).

DISCUSSION

Our study demonstrates the presence of an inverse correlation between SHBG concentrations and BMI both in hirsute (PCOS and IH) and in nonhirsute eumenorrheic normal women. This suggests that obesity can influence SHBG concentrations and increase fT levels.[1,2,5,11,18,19] The fact that this correlation was evident in each of three groups studied demonstrates that it is not restricted to hyperandrogenic states. However, a significant correlation between SHBG and fT levels was evident in all groups. In each group, SHBG levels were significantly lower and serum fT concentrations were higher in obese than in non-obese women (Table 1). In previous studies, the finding of increased fT level in obese C and IH subjects has been related to an increased production rate of androgens.[1,4,5,18] It has been suggested that adrenal steroids such as cortisol, DHEAS, and A[4,5,18] are overproduced in obesity. We did not observe any significant difference in serum cortisol (data not shown), DHEAS, or A concentrations between obese and non-obese women in C, IH, or PCOS groups.

Moreover, an inverse correlation between SHBG and BMI in C and IH obese women has been observed. These data suggest that excess body weight per se can induce a decrease in SHBG and consequently an increase in fT levels, independently of the presence of different androgen levels and of other causes of increased androgen production. The mechanisms involved in SHBG reduction in obesity have not yet been clarified. Obesity leads to a mild hyperestrogenism, but an increased hepatic production of SHBG has been observed only at supraphysiologic E2 levels.[5] By contrast, androgens decrease circulating levels of SHBG by acting on its hepatic synthesis. It is possible that obesity-related hyperandrogenemia (whether adrenal or ovarian) leads to a decrease in SHBG levels, a greater metabolic clearance rate of testosterone, and a new sex hormone equilibrium.[4,5]

It is well known that an excess of fat mass can lead to an increase in circulating insulin levels and can influence steroid hormone metabolism.[4,5,15] Hyperinsulinemia has been regarded as a possible cause of SHBG reduction and of ovarian hyperandrogenism.[4,5,10,12,13] Several studies have demonstrated a significant correlation between fasting or glucose-stimulated insulin levels and SHBG concentrations[4,10,15,16,20,21] or hyperandrogenism in PCOS patients[4,22] and in normal males[23] and females.[1,4,5,10-13,16,22,24] However, others have not found any significant correlation.[25,26] Moreover, although there is experimental evidence that insulin can decrease basal and stimulated SHBG production by liver cells in vitro,[27] no clear effect of hyperinsulinemia on ovarian androgen production or SHBG levels has been demonstrated in vivo.[4,26,28] There are data supporting the idea that high insulin levels in hyperandrogenic patients, as in obese subjects, reflect some degree of insulin resistance.[4,5,10,16] However, an individual might have insulin resistance in terms of glucose transport, yet remain sensitive to the action of insulin on SHBG.[10] Unfortunately, serum insulin levels were not examined in the current study.

Nutritional factors, particularly a high-lipid, low-fiber diet,[4,5] and other endocrine modifications, such as an increase in endorphins,[4] a reduction in insulin-like growth factor binding protein-1,[4,15,16] and an increase in insulin-like growth factor-I,[4,10,15] may also play a role in the alterations of sex hormone metabolism observed in obese subjects.

When considering obese PCOS women alone, the correlation between SHBG levels and BMI was no longer significant in our study, confirming that these women have

Table 3. Hormonal Concentrations in Upper-Body and Lower-Body Obese PCOS, IH, and C Women

	PCOS		IH		C	
Hormone	Upper-Body	Lower-Body	Upper-Body	Lower-Body	Upper-Body	Lower-Body
LH (mIU/mL)	4.8 ± 3.1	4.7 ± 3.7	2.6 ± 0.9	2.2 ± 0.5	2.6 ± 1.3	2.5 ± 1.2
FSH (mIU/mL)	4.5 ± 1.6	3.5 ± 1.3	4.1 ± 1.7	3.9 ± 1.4	4.4 ± 1.8	6.3 ± 3.6
E2 (pg/mL)	30.8 ± 16.3	46.3 ± 42	30 ± 21.6	39.9 ± 31.4	43.6 ± 27.2	43.3 ± 40.9
fT (pg/mL)	4.2 ± 1.2	3.9 ± 1.4	2.5 ± 0.6	1.7 ± 0.5	2.2 ± 0.9	1.15 ± 0.5
SHBG (nmol/L)	28.3 ± 18.5	26.5 ± 10.8	39.3 ± 14.9	47.1 ± 16.0	46.5 ± 23.3	62.2 ± 27.5
A (ng/mL)	2.5 ± 0.9	3.2 ± 1.0	2.2 ± 1.4	1.6 ± 0.7	1.6 ± 0.9	1.2 ± 0.4
DHEAS (μg/mL)	2.4 ± 0.8	2.7 ± 0.7	2.4 ± 0.5	2.1 ± 0.8	1.9 ± 1.0	1.9 ± 0.7

an independent source of androgen excess that may blur the differences in fT and SHBG related to obesity.

Our study also demonstrated a significant difference in fT and SHBG levels between normal eumenorrheic women with upper-body obesity and those with lower-body obesity (Table 3). This pattern was also observed in IH patients.

In conclusion, obesity is associated with low serum SHBG and high serum fT levels in C, IH, and PCOS women. Eumenorrheic obese women exhibited fT levels similar to levels in IH subjects. It is our opinion that obesity—in particular upper-body obesity—directly or through other related factors can influence SHBG concentration and facilitate the development of hyperandrogenic milieu. Clarification of the pathogenetic mechanisms underlying the decrease in SHBG and the increase in fT levels in obesity warrants further investigation.

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