Determinants of Sex Hormone–Binding Globulin Blood Concentrations in Premenopausal and Postmenopausal Women With Different Estrogen Status

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In women, sex hormone–binding globulin (SHBG) concentrations are the result of a balanced effect of stimulatory and inhibitory factors. Estrogens represent the principal stimulatory hormones, whereas androgens, insulin, excess body fat, and the pattern of body fat distribution have inhibitory effects. Menopause is characterized by major changes in blood sex steroid concentrations, notably a marked reduction of estradiol levels. In this study, we therefore investigated the relationship between hormonal and nonhormonal regulatory factors of SHBG and its blood levels in two groups of premenopausal and postmenopausal women characterized by normal-high or reduced estrogen concentrations. The data were obtained from an analysis of the cross-sectional database obtained during the first survey of the Virgilio-Menopause-Health Project, an epidemiologic longitudinal study aimed at investigating the impact of menopause on body weight, fat distribution, and related major metabolic, hormonal, and cardiovascular risk factors. A total of 329 women, 133 in premenopause and 196 in postmenopause without diabetes, thyroid diseases, or relevant cardiovascular, renal, and hepatic dysfunction, were included in the study. A clinical history (including dietary and physical-activity habits), anthropometry (body mass index [BMI], waist to hip ratio [WHR], and bioelectrical impedance analysis [BIA]), and morning blood samples in the fasting state for sex hormones, insulin, and biochemistry were available for all the women. Premenopausal and postmenopausal women showed no significant difference in SHBG concentrations (38.7 ± 17.9 *v* 36.6 ± 17.5 nmol/L, respectively). On the contrary, postmenopausal women were characterized by a marked reduction of estradiol levels and significantly lower levels of testosterone. After adjusting for age, insulin was lower and the glucose to insulin ratio was higher in postmenopause than in premenopause. Age-adjusted values for all anthropometric parameters were not significantly different in the two groups. In simple correlation models, SHBG was significantly and negatively correlated with BMI, WHR, and insulin and testosterone levels in both premenopausal and postmenopausal women, whereas estradiol levels correlated positively and significantly with SHBG only in the premenopausal group. A significant positive correlation between the glucose to insulin ratio and SHBG was present in both groups. Using multiple regression models, 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. In conclusion, this study indicates that (1) there is no significant difference in SHBG blood concentrations between premenopause and postmenopause; (2) SHBG values are correlated positively with estradiol and negatively with insulin and testosterone concentrations, but the predictive value of these variabiles on SHBG appears to be different in premenopause and postmenopause; and (3) SHBG levels decrease with increasing WHRs, particularly in the postmenopausal group. Therefore, determinants of SHBG blood concentrations are likely to change on passing from premenopausal to postmenopausal status. In particular, there seems to be a threshold level for which estradiol is an important determinant of SHBG blood concentrations.
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IN WOMEN, sex hormone–binding globulin (SHBG) blood concentrations are regulated by a complex of stimulatory and inhibitory factors. Among the former, estrogens seem to have a prominent role. In fact, they can increase SHBG hepatic synthesis and blood levels in vitro[1] and in vivo.[2] Moreover, it is well known that conditions with endogenous hyperestrogenemia such as pregnancy are associated with elevated SHBG levels.[2] Thyroid hormones are also capable of increasing SHBG both in vitro[3] and in vivo,[4] at least in supraphysiologic concentrations. Among inhibitory factors, androgens seem to play a key role. SHBGs are in fact typically reduced in hyperandrogenic states[2] and following exogenous androgen administration.[5] In fact, the question of whether sex steroids can regulate SHBG even in physiologic conditions is still under debate, since physiologic changes in sex steroid levels do not always correlate with changes in SHBG.[6]

In the last decade, a large amount of data have demonstrated that insulin can be an important inhibiting factor of SHBG synthesis.[7] Numerous epidemiologic studies have in fact demonstrated a significantly negative correlation between insulin concentrations and SHBG blood levels, suggesting a cause-and-effect relationship.[8] Moreover, studies in vitro have shown that insulin can inhibit hepatic SHBG synthesis,[1] and suppression[9] or stimulation[10] of insulin secretion in vivo has been found to be inversely associated with changes of SHBG concentrations, particulary in hyperandrogenic women with polycystic ovaries.

In vivo, it is difficult to adequately define the complex interaction of all these factors, due to the frequent association in the same women of hyperinsulinemia, hyperandrogenism, and increased estrogen production.[11] For example, reduced SHBG levels in women are commonly associated with obesity,[11] type II diabetes,[12] hyperandrogenism (such as polycystic ovary syndrome),[13] and cardiovascular diseases,[14] all conditions known to

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be frequently characterized by hyperinsulinemia and insulin resistance.[15]

In addition, reduced SHBG levels are also independently associated with abdominal fat distribution, particularly in obese women, which suggests that the relative increase of free androgens at the tissue level may play a role in the expansion of visceral fat in susceptible individuals.[15]

The role of the estrogens in these conditions is unclear. In obese women who have a high estrogen production rate, SHBG levels are usually reduced proportionally to the increase in body weight and particularly in abdominal fat.[11] The impact of a physiologic change of estrogens, for example, as occurs in the transition from premenopause to postmenopause, has not been adequately investigated in published epidemiologic studies, and the available data appear to be largely inconclusive.[14,16]

In this study, we therefore investigated the interrelationship between SHBG, androgen, estrogen, and insulin blood levels, and that of other factors such as body weight and fat distribution, in two large groups of middle-aged premenopausal and postmenopausal women characterized by physiologically normal-high or low estrogen concentrations, respectively.

SUBJECTS AND METHODS

Subjects

Data for this study were obtained from the Virgilio-Menopause-Health Project database, the general characteristics of which have been reported in previous studies.[17] Briefly, this is an epidemiologic longitudinal study that we began in 1990 to investigate the impact of menopause on body weight, fat distribution, and related major metabolic, hormonal, and cardiovascular risk factors. The study included all women born between January 1st, 1932, and December 31st, 1946, and living in the town of Virgilio, Mantua, Italy. Only women within an age range of 7 years older or 7 years younger with respect to this limit were invited to take part in the project. This range was selected to include only women in the late fertile age and early postmenopausal life so as to prevent possible age-related bias, since age per se has a great effect on body composition and fat distribution, particularly in elderly people.[18]

A total of 596 women (62.6%) participated in the study. According to menopausal status (see below), women were divided into three groups: premenopause, perimenopause, and postmenopause. For the purposes of this study, only women with premenopausal or postmenopausal status were considered. From the original sample group, based on clinical history and laboratory data, all women with overt diabetes, thyroid disease, or relevant cardiovascular, renal, hepatic, or systemic diseases were excluded from the analysis. Women taking medications (including estrogens and progestagens) known to interfere with sex steroid, glucose, or insulin secretion and/or metabolism were excluded. The data presented here are the results of an analysis of a cross-sectional database obtained during the first survey of the Project, and refer to a final sample of 329 women, 133 in the premenopause group and 196 in the postmenopause group.

Study Protocol

All women recruited into the study were evaluated in the morning after 12 hours of fasting. All evaluations were performed by the same well-trained investigator (O.T.) for the entire duration of the study. They included a collection of blood samples (40 mL) for hormonal and biochemical determinations. In menstruating women, blood samples were obtained randomly throughout the menstrual cycle. The date of the previous bleeding was also recorded, for an appropriate definition of the cycle phase in which the samples were taken. After blood samples had been drawn, they were maintained at room temperature and centrifuged within 60 minutes. They were immediately frozen at −20°C and moved into a −76°C freezer within 1 or 2 days.

In the evaluation, we used a precoded questionnaire[17] including a full clinical and family history, with socioeconomic and personal information, habitual or current drug use, diet, physical activity and smoking habits, lifetime weight variations, and careful recording of principal gynecologic events.

Anthropometric Measurements

Several anthropometric measurements were also obtained with the women in underwear. Height (to the nearest centimeter) and weight (to the nearest 0.5 kg) were recorded. Body mass index (BMI) was calculated by dividing body weight in kilograms, by height in meters squared. Body circumferences were measured in the standing position at the waist[19] (smallest circumference between lateral costal margin and iliac crest) and hips (widest circumference over the greater trochanters) and their ratio was used as an index of body fat distribution.[19] We also performed bioelectrical impedance analysis (BIA) in 279 women (84.8%), since the BIA apparatus only became available 2 months after the study had begun. BIA was performed using a tetrapolar phase-sensitive impedance plethysmograph (50 kHz) BIA 101S (Akern RJL Systems, Florence, Italy). BIA is a safe and validated method of estimating body fluids and free fat mass (FFM) in humans.[20] Measurements were made while subjects lay comfortably on a bed. All procedures were performed according to the manufacturer's instructions. Fat mass (FM) was calculated by subtracting FFM from body weight.

Definition of Menopausal Status

Definition of the menopausal status was performed in accordance with widely used criteria.[21] Women in amenorrhea for at least 12 months with estradiol levels less than 150 pmol/L and follicle-stimulating hormone (FSH) levels higher than 15 IU/L and women who had undergone a bilateral ovariectomy and hysterectomy and were amenorrheic were included in the postmenopausal group. In this group, the time after menopause ranged from 1 to 26 years, with a mean ± SD of 6.6 ± 5.6 years. Those presenting with normal menses or who in any case reported at least 10 menstrual cycles in the antecedent year and were without climacteric-related symptoms (such as hot flashes, bleeding irregularities, and mood fluctuations) were included in the premenopausal group.

Hormones and Biochemistry

All hormones were determined in duplicate on serum samples stored at −76°C until assayed. Gonadotropins (standard: leutinizing hormone 1° International Reference Preparation [IRP] 68/40; FSH 2° IRP 78/549) were determined by radioimmunoassay using reagents purchased from Tosoh (Tokyo, Japan). Testosterone and estradiol were determined with reagents purchased from, respectively, Diagnostic System Laboratories (Webster, TX) and Diagnostic Products (Los Angeles, CA). SHBG level was measured with a noncompetitive liquid-phase immunoradiometric assay with reagents purchased from Pharmos Diagnostic (Oulunsalo, Finland). Insulin was determined using reagents purchased from Eiken Chemical (Tokyo, Japan). Blood glucose concentrations were determined immediately after blood samples had been drawn, by the glucose oxidase method. The fasting glucose to insulin ratio was used as an index of insulin sensitivity, as previously described.[22] All analytical data related to hormone assays have already been reported elsewhere.[18]

Statistics

Results are reported as the mean ± SD unless otherwise indicated. Data that did not fit the normal distribution as assessed by the Kolmogorov-Smirnov test[23] were adequately normalized using polyno-

mial and/or logarithmic transformations. Simple regression analysis of all included variables versus age and SHBG values was performed. Comparisons between the two groups were analyzed by ANCOVA[24] to adjust for age. Stepwise multiple regression analyses[24] considering SHBG as a dependent variable were also performed. All statistical evaluations were performed using the SPSS/PC+ statistical package (SPSS, Chicago, IL) on a personal computer.

RESULTS

General Characteristics

Postmenopausal women were significantly ($P < .001$) older than premenopausal women (Table 1). All anthropometric indices except FFM were significantly ($P < .01$) and positively correlated with age. However, after adjusting for age, body weight and BMI were slightly but significantly higher in postmenopausal than in premenopausal women, but these differences were significantly smaller than expected on the basis of the relationship between these parameters and age. However, both FFM and FM were not significantly different between the two groups after adjusting for age. There was also no age-adjusted significant difference in the waist to hip ratio (WHR) between the two groups, suggesting no independent effect of menopausal status on the pattern of body fat distribution (Table 1).

Hormones and Biochemistry

SHBG concentrations were similar in both groups (38.7 ± 17.9 nmol/L for premenopausal and 36.6 ± 17.5 nmol/L for postmenopausal, P = NS). Postmenopausal women had significantly higher levels of gonadotropins ($P < .001$) and lower levels of estradiol ($P < .001$). Testosterone concentrations were also lower in postmenopause than in premenopause ($P < .054$). Comparisons of all variables between the two groups were performed after adjusting for age, although SHBG, gonadotropins, and testosterone (but not estradiol) levels were not correlated with age. It is unlikely that these results were dependent in some way on the fact that in menstruating women blood samples had been drawn randomly throughout the menstrual cycle. In fact, they were obtained, on average, on day 14.8 (median, 14.0) of the cycle, which suggests that greater than half of the premenopausal women were examined in the follicular phase. Moreover, the majority of the premenopausal group had a normal cycle length. In fact, of 133 women included in the premenopausal group, 107 had 12 cycles during the year before the survey, nine had 10 or 11 cycles, and two had 13 and 15 cycles, respectively; 15 of them were in amenorrhea because they had a hysterectomy without ovariectomy (all for fibroma of the uterus). When data obtained from all other women examined in the luteal phase or at random in those presenting with oligomenorrhea were excluded, no significantly different trend in gonadotropin and estradiol was observed. Insulin and glucose concentrations but not the glucose to insulin molar ratio were also significantly correlated with age. After adjusting for age, mean values for insulin ($P = .004$) and glucose ($P = .039$) were significantly lower and the glucose to insulin ratio was higher ($P = .009$) in postmenopausal versus premenopausal women (Table 2).

Table 1. Anthropometric Variables (mean ± SD) in Premenopausal and Postmenopausal Women

Variable	Menopausal Status: Premenopause (n = 133)	Menopausal Status: Postmenopause (n = 196)	Regression *v* Age (*P*)	ANCOVA (*P*)*
Age (yr)	46.5 ± 2.6	52.4 ± 3.6		.001
Body weight (kg)	63.9 ± 9.1	64.8 ± 11.3	.001	.049
BMI (kg/m²)	25.7 ± 3.5 (130)	25.9 ± 4.4	.000	.017
WHR	0.79 ± 0.06	0.82 ± 0.07 (194)	.000	.450
FFM (kg)	42.0 ± 3.3 (118)	41.5 ± 3.5 (161)	.143	.074
FM (kg)	21.6 ± 7.2 (118)	22.7 ± 5.1 (161)	.002	NS

NOTE. Numbers in parentheses refer to the number of observations when different from the total number of women in each group.

*After adjustment for age values. Age was analyzed by ANOVA without adjustment.

Correlations Between SHBG, Hormones, and Anthropometry

In simple correlation models, SHBG concentrations were significantly and negatively correlated with BMI, WHR, and insulin and testosterone concentrations in both premenopausal and postmenopausal women (Table 3). On the contrary, SHBG was significantly and positively correlated with estradiol levels, but only in the premenopausal group. Moreover, in both groups there was a positive correlation between SHBG values and the glucose to insulin ratio.

Using multiple regression models, in the whole sample of women considered as a group, SHBG concentrations were correlated significantly and positively with estradiol and negatively with insulin and testosterone concentrations and with WHR. When the same analysis was applied in premenopausal women, 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 had a significant negative correlation with the WHR, whereas the relationship with estradiol was not significant; moreover, its relationship with testosterone and insulin, although significant, became less marked (Table 4).

DISCUSSION

Although postmenopausal women had lower SHBG blood concentrations than the premenopausal group, this difference was not significant even when the comparison was made after adjusting for age. Our data therefore seem to indicate that menopause per se is not associated with significant changes in blood concentrations of SHBG. In a recent review, Rossner[2] included menopause among the conditions characterized by decreased SHBG levels. This assumption was based on a few epidemiologic studies, the results of which appeared to be inconclusive. In fact, whereas some reported a negative correlation between age and SHBG,[14] others found an inverse relationship.[16,25] However, regardless of their conclusions, no study has clearly demonstrated whether menopause per se or related factors may have an independent effect on SHBG synthesis, transport, or metabolism. Menopause is a condition associated with important changes in the concentrations of sex steroids, which are thought to represent the main factors regulating SHBG levels. In particular, on passing from premenopause to postmenopause, there is a great decrease in estradiol concentrations, due to decreased aromatase activity in the ovaries.[26]

Table 2. Sex Hormone, SHBG, Insulin, and Glucose Blood Concentrations (mean ± SD) in Premenopausal and Postmenopausal Women

Hormone	Menopausal Status: Premenopause (n = 133)	Menopausal Status: Postmenopause (n = 196)	Regression v Age (P)	ANCOVA (P)*
SHBG (nmol/L)	38.7 ± 17.9 (116)	36.6 ± 17.5 (178)	.090	NS
LH (IU/L)	5.5 ± 5.9 (114)	26.7 ± 12.0 (168)	.311	<.001
FSH (IU/L)	10.2 ± 7.3 (114)	100.3 ± 35.4 (168)	.208	<.001
Testosterone (nmol/L)	0.98 ± 0.49 (113)	0.79 ± 0.40 (167)	.230	.054
Estradiol (pmol/L)	356.2 ± 264.9 (114)	56.4 ± 57.0 (166)†	.017	<.001
Insulin (pmol/L)	60.7 ± 41.5 (114)	52.5 ± 33.1 (166)	.061	.004
Glucose (mmol/L)	4.91 ± 0.57 (129)	4.87 ± 0.58	.032	.039
Glucose to insulin ratio	0.10 ± 0.06 (113)	0.12 ± 0.06 (166)	.155	.009

NOTE. Numbers in parentheses refer to the number of observations when different from the total number of women in each group.

*After adjustment for age values.

†The high SD in this group was due to the presence of 3 women with estradiol values of 282, 319, and 326 pmol/L, respectively. These values were in fact higher than those used to define postmenopausal status (estradiol values <150 pmol/L). Investigation of the individual files led to the conclusion that, based on clinical and other hormonal data, these women were in postmenopause. Therefore, they were maintained in the file.

Additionally, there is a less important but significant decrease in ovarian androgen production, which can account for the small reduction in both androstenedione and testosterone levels after menopause.[27,28] Androgen blood concentrations are then maintained by the adrenals, which are responsible for approximatively 95% of androstenedione production in postmenopausal women. Our findings are consistent with these data, since postmenopause estradiol blood levels decreased by approximatively 85% and testosterone levels by 20%. Therefore, postmenopausal women have an increased androgen to estrogen ratio.

In this study, both testosterone (negative) and estradiol

Table 3. Simple Correlation Between Several Variables and SHBG Blood Levels

Independent Variable	Group: Premenopause	Group: Postmenopause	All
Age	−.060	−.120	−.114
Body weight	−.265†	−.239†	−.244†
BMI	−.268†	−.268†	−.270†
FFM	−.197*	−.060	−.106
FM	−.185	−.258†	−.235
WHR	−.287†	−.266†	−.280†
Testosterone	−.338†	−.208†	−.237†
Estradiol	.251†	.102	.146*
Insulin	−.359†	−.344†	−.339†
Glucose	−.288†	−.110	−.165†
Glucose to insulin ratio	.330†	.333†	.320†

*$P < .05$.

†$P < .01$.

Table 4. Stepwise Multiple Regression Analysis Versus SHBG Levels (dependent variable) Applied in the Whole Sample of Women and the Premenopausal and Postmenopausal Groups Separately

Independent Variable	Multiple r	P	t	P
All women (premenopausal + postmenopausal)	.490	<.0001		
Estradiol			4.014	<.0001
Insulin			−4.779	<.0001
Testosterone			−5.567	<.0001
WHR			−2.380	.0180
Premenopausal women	.592	<.0001		
Estradiol			3.744	.0003
Insulin			−3.910	.0002
Testosterone			−4.713	<.0001
WHR			−1.204	NS
Postmenopausal women	.452	<.0001		
Estradiol			1.900	.0593
Insulin			−2.893	.0044
Testosterone			−3.587	.0004
WHR			−2.156	.0326

NOTE. Only independent variables with significant P values were included in the analysis.

(positive) levels were significantly correlated with SHBG. The relationship with estradiol was in fact much weaker in postmenopausal than in premenopausal women, which suggests the possibility that the positive effect of estradiol on SHBG synthesis may be notably reduced in postmenopausal women. This may support the concept that a threshold level (~150 pmol/L?) may exist by which estradiol is an important determinant of SHBG blood concentrations. On the contrary, the negative correlation with testosterone was maintained in both groups, although in postmenopausal women the correlation was slightly lower than in premenopausal women. Since no significant variation in SHBG was found on passing from premenopause to postmenopause, whereas testosterone levels tended to decrease slightly but significantly, these findings may be consistent with the hypothesis that the negative impact of testosterone on SHBG synthesis and metabolism in postmenopausal women is probably smaller than during premenopausal life.

Unexpectedly, we found a modest but significant reduction of mean fasting insulin blood levels after menopause. This was associated with a parallel reduction of the glucose to insulin ratio, an index of peripheral insulin sensitivity.[22] This suggests that during early postmenopause, there may be increased insulin sensitivity, which appears to be independent of changes in body composition, fat distribution, and age. In fact, insulin concentrations did not correlate with age, and the correlation with BMI and WHR was positive. Other factors related to menopausal events are therefore probably involved and obviously require further investigation. The relationship between insulin and SHBG in both premenopausal and postmenopausal women was negative, in accordance with the inhibiting capacity of insulin on SHBG synthesis, which has been demonstrated both in vitro[1] and in vivo.[9] However, the predictive value of insulin levels on SHBG in postmenopause was lower than during premenopause. This is probably due to a reduction in insulin concentrations during early postmenopausal life.

Of all the anthropometric parameters, only WHR was significantly and negatively correlated with SHBG concentrations in

the postmenopausal group but not in the premenopausal group. Many studies have demonstrated a significant positive correlation between age and WHR,[18] and our data are in agreement with previous findings, suggesting that age and related factors play an important role in determining changes in body fat distribution patterns during life. Our previous data seem to indicate that the menopause per se fails to affect body fat distribution.[17] Since abdominal body fat distribution is associated with both hyperinsulinemia and an increased free testosterone fraction,[15] it is possible that the negative correlation between WHR and SHBG may be primarily mediated by these factors.

In conclusion, this study indicates that (1) there is no significant difference in SHBG blood concentrations between premenopause and postmenopause; (2) SHBG values are correlated positively with estradiol and negatively with insulin and testosterone concentrations, but the predictive value of these hormones on SHBG appears to be different in premenopause and postmenopause; and (3) levels of SHBG decrease with increasing WHR, particularly in postmenopause. Therefore, determinants of SHBG blood concentrations are likely to change on passing from premenopausal to postmenopausal status.

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REFERENCES

1. Plymate SR, Matej LA, Jones RE, et al: Inhibition of sex hormone–binding globulin production in the human hepatoma (Hep G2) cell line by insulin and prolactin. J Clin Endocrinol Metab 67:460-464, 1988

2. Rossner W: The functions of corticosteroid-binding globulin and sex hormone–binding globulin: Recent advances. Endocr Rev 11:80-91, 1990

3. Raggat LE, Rozanne BB, Hamblin PS, et al: Effects of thyroid hormone on sex hormone–binding globulin gene expression in human cells. J Clin Endocrinol Metab 75:116-120, 1992

4. Faber J, Perrild H, Johansen J: Bone gla and sex hormone–binding globulin in nontoxic goiter: Parameters for metabolic status at the tissue level. J Clin Endocrinol Metab 70:49-55, 1990

5. Plymate SR, Leonard JM, Paulsen CA, et al: Sex hormone–binding globulin changes with androgen replacement. J Clin Endocrinol Metab 57:645-648, 1983

6. von Schultz B, Carlsrom K: On the regulation of sex-hormone–binding globulin: challenge of an old dogma and outlines of an alternative mechanism. J Steroid Biochem 32:327-334, 1989

7. Nestler JE: Sex hormone–binding globulin: A marker for hyperinsulinemia and/or insulin resistance? J Clin Endocrinol Metab 76:273-274, 1993 (editorial)

8. Preziosi P, Barreth-Connor E, Papoz L, et al: Interrelation between plasma sex hormone–binding globulin and plasma insulin in healthy adult women: The Telecom Study. J Clin Endocrinol Metab 76:283-287, 1993

9. Nestler JE, Clore JN, Blackard WG: Suppression of serum insulin by diazoxide reduces serum testosterone levels in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 68:1027-1032, 1989

10. Nestler JE, Clore JN, Strauss JF III, et al: The effects of hyperinsulinemia on serum testosterone, progesterone, dehydroepiandrosterone sulfate, and cortisol levels in normal women and in a woman with hyperandrogenism, insulin resistance, and acanthosis nigricans. J Clin Endocrinol Metab 64:180-184, 1987

11. Glass AR, Burman KD, Dahms WT, et al: Endocrine function in human obesity. Metabolism 30:89-104, 1981

12. Lindsted G, Lundberg PA, Lapidus L, et al: Low sex-hormone–binding globulin concentration as independent risk factor for development of NIDDM. Diabetes 40:123-128, 1991

13. Franks S: Polycystic ovary syndrome: A changing perspective. Clin Endocrinol (Oxf) 31:87-120, 1989

14. Lapidus L, Lindstedt G, Lundberg PA, et al: Concentrations of sex-hormone binding globulin and corticosteroid binding globulin in serum in relation to cardiovascular risk factors and to 12-year incidence of cardiovascular disease and overall mortality in postmenopausal women. Clin Chem 32:146-152, 1986

15. Bjorntorp P: Metabolic implications of body fat distribution. Diabetes Care 12:1132-1143, 1991

16. Maruyama Y, Aoki N, Suzuki Y, et al: Variation with age in the levels of sex steroid–binding plasma protein as determined by radioimmunoassay. Acta Endocrinol (Copenh) 106:428-432, 1984

17. Pasquali R, Casimirri F, Morselli Labate AM, et al: Body weight, fat distribution and the menopausal status in women. Int J Obes 18:614-621, 1984

18. Bouchard C, Després JP, Mauriège P: Genetic and nongenetic determinants of regional fat distribution. Endocr Rev 14:72-93, 1983

19. WHO Document: Measuring obesity—Classification and Description of Anthropometric Data. Copenhagen, Denmark, WHO Regional Office for Europe, Eur/ICP/NUT 125-0612 v, 1988

20. Segal KR, Van Loan M, Fitzgerald P, et al: Lean body mass estimation by bioelectrical impedance analysis: Four site cross-validation study. Am J Clin Nutr 47:7-14, 1988

21. Odell WD: The menopause, in DeGroot LJ (ed): Endocrinology. Philadelphia, PA, Saunders, 1989, pp 2009-2018

22. Bergman RN, Finegood DT, Ader M: Assessment of insulin sensitivity in vivo. Endocr Rev 6:45-86, 1985

23. Siegel S: Nonparametric Statistics for the Behavioral Sciences. New York, NY, McGraw-Hill, 1956

24. Snedecor NR, Cochram WG: Statistical Methods (ed 8). Ames, IA, Iowa State University Press, 1989

25. Siiteri PK, Murai JT, Hammond GL, et al: The serum transport of steroid hormones. Recent Prog Horm Res 38:457-510, 1982

26. Mattingly RF, Huang WY: Steroidogenesis of the menopause and postmenopausal ovary. Am J Obstet Gynecol 103:679, 1969

27. Jaffe RB: The menopause and perimenopausal period, in Yen SSC, Jaffe RB (eds): Reproductive Endocrinology: Physiology, Pathophysiology and Clinical Management (ed 2). Philadelphia, PA, Saunders, 1986, pp 406-423

28. Carr BR, MacDonald PC: Estrogen treatment of postmenopausal women. Adv Intern Med 28:491-508, 1983