Hyperinsulinemia and Sex Hormones in Healthy Premenopausal Women: Relative Contribution of Obesity, Obesity Type, and Duration of Obesity

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Insulin secretion in response to an oral glucose tolerance test (OGTT) and sex hormone levels (free testosterone, androstenedione, dehydroepiandrosterone sulfate [DHEAS], estradiol, and sex hormone–binding globulin [SHBG]) were evaluated in 49 healthy obese premenopausal women (body mass index [BMI], 30 to 50.6 kg/m^2) and 21 control subjects (BMI, 17.8 to 24.0 kg/m^2) with normal glucose tolerance and without signs of hyperandrogenism. Obese women were divided into two groups according to waist to hip ratio (WHR): 27 subjects with upper-body obesity (WHR > 0.85) and 22 subjects with lower-body obesity (WHR < 0.8). Both fasting and glucose-induced insulin levels were higher in women with upper-body obesity than in controls ($P < .001$) and those with lower-body obesity ($P < .001$). Hyperandrogenism was observed in women with upper-body obesity, as evident by significantly elevated free testosterone ($P < .05$ *v* controls and subjects with lower-body obesity) and decreased SHBG ($P < .001$ *v* controls). The most important independent determinants of fasting insulin levels were BMI ($P < .01$) and the ratio of DHEAS to free testosterone ($P < .01$). The most important determinants of cumulative insulin response were WHR ($P < .0005$), duration of obesity ($P < .01$), and androstenedione levels ($P < .01$). In conclusion, in healthy obese premenopausal women without clinical signs of hyperandrogenism, a high BMI and more pronounced upper-body fat localization resulted in hyperinsulinemia and hyperandrogenism. The duration of obesity exaggerated the glucose-induced insulin level and cumulative insulin response independently of the degree of obesity and obesity type. The ratio of DHEAS to free testosterone was an independent determinant of fasting insulin concentration. Furthermore, the ratio of DHEAS to free testosterone rather than either of these androgens alone may be important in the regulation of insulin action in women.

OBESITY is one of the most important risk factors for non–insulin-dependent diabetes mellitus (NIDDM) and cardiovascular disease.[1-4] There is increasing evidence that many complications of obesity, eg, diabetes, gout, hypertension, and an increasing incidence of endocrine-related neoplasms such as carcinoma of the endometrium, are more common in patients with upper-body obesity.[5-9]

The coexistence of insulin resistance and hyperandrogenism in women has been described frequently, mainly in women with the polycystic ovary syndrome (PCO).[10,11] Abdominal fat distribution has been found to be associated with insulin resistance and the incidence of NIDDM.[12] Women with abdominal fat distribution exhibit other android characteristics in addition to male-pattern adipose tissue localization. Elevated plasma androgen and decreased sex hormone–binding globulin (SHBG), resulting in increased tissue availability of unbound hormones, are more common in women with upper-body obesity.[13]

These characteristics are highly interrelated, but opinions diverge on the nature of the interrelationship. The hypothesis that has gained the most support is that elevated insulin levels found in insulin-resistant states can stimulate ovarian androgen production and suppress hepatic SHBG production (reviewed in Poretsky[14]). However, others have provided evidence to suggest that hyperandrogenism can induce insulin resistance (reviewed in Bjorntorp[15]). Low SHBG, presumably a sign of hyperandrogenicity, has been shown to be a strong independent risk factor for the development of NIDDM in women.[16,17]

There are thus several possible mechanisms by which upper-body obesity, hyperandrogenism, and insulin resistance may be causally associated with the development of NIDDM. In present study, we evaluated the individual and combined contributions and interrelationships of overall obesity, obesity type, duration of obesity, and androgens to insulin levels in healthy premenopausal women.

SUBJECTS AND METHODS

Seventy healthy premenopausal women without diabetes mellitus, hirsutism, virilism, acanthosis nigricans, cardiac disease, hypertension, or malignancy were included in the study. They were neither dieting at the time of study nor participating regularly in an exercise program. All obese women attended the outpatient clinic. Studies were performed at the Department of Internal Disease, Division of Endocrinology, Clinical Hospital Osijek. Normal-weight women were volunteers and hospital staff with regular menstruation, no hirsutism, and normal ovaries on pelvic ultrasound. All subjects provided informed consent before participating.

A detailed history and physical examination were performed before the study. Serum renal, hepatic, and thyroid function were assessed by routine laboratory tests. An electrocardiogram and pelvic ultrasound examination were also obtained. All studies for the subjects were normal. Additional criteria for subject inclusion were (1) normal cycling menstrual history, (2) stable body weight for at least 2 months before the study, (3) no previous use of oral contraceptives, and (4) no drug intake for at least 1 month before the study. All women were studied during the follicular phase (between cycle days 4 and 12).

The subjects had a wide range of adiposity, with a weight range of 48.6 to 136 kg, ie, 79% to 205% of ideal body weight according to the Metropolitan Life Insurance Tables. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, and ranged from 17.8 to 50.6 kg/m^2. Waist circumference was measured in the standing position at the halfway point from the lower rib margin and iliac crest, and hip circumference over the widest part of the hip

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region. The waist to hip ratio (WHR) was calculated as described elsewhere.[18]

Subjects were divided into three groups according to BMI and WHR: (1) 27 women with upper-body obesity (BMI > 30 kg/m^2 and WHR ≥ 0.85), (2) 22 women with lower-body obesity (BMI > 30 kg/m^2 and WHR < 0.80), and (3) 21 normal-weight healthy women in the control group (BMI, 17.8 to 24.0 kg/m^2). Subjects with a WHR between 0.8 and 0.85 were not included in the study. Only subjects with normal glucose tolerance according to World Health Organization criteria[19] were included in the study. Smoking habits were recorded as the average number of cigarettes smoked per day. Smoking status was randomly distributed between groups: 15 of 70 women were smokers, and in each group five were smokers. There were no differences in the number of smokers or in the average number of smoked cigarettes per day between examined groups. The duration of obesity was determined as the time since significant obesity occurred. It was obtained solely as anamnestic data for the onset of obesity, ie, the time when body weight exceeded 20% of the ideal weight. Although it was a matter of subjective recall, we have tried to diminish the large subjective element with carefully phrased questions about body weight in this period and by checking body weight in the medical documentation (local general practice register). Clinical characteristics of the 70 premenopausal women are shown in Table 1.

After an overnight fast, baseline blood samples were collected for hormone assays. Then, an oral glucose tolerance test (OGTT) was performed. After ingestion of 75 g glucose, plasma samples were obtained at 0, 60, and 120 minutes. Samples were analyzed for glucose, insulin, and C-peptide concentrations. Serum was obtained by centrifugation and stored until analysis. The cumulative glucose, insulin, and C-peptide responses (area under the OGTT curve) were calculated as the area under the trapezium described by glucose or insulin measurements at 0, 60, and 120 minutes. Insulin clearance was estimated from time 0 C-peptide to insulin ratios and fractional hepatic insulin extraction (FEI) according the formula, (C-peptide − insulin)/C-peptide × 100.[20]

A specific radioimmunoassay was used for determination of the hormones androstenedione (Diagnostic System Laboratories), DHEAS (Immunotech International), free testosterone (Diagnostic Products), estradiol (Sorin Biomedica), and SHBG (Medscand Diagnostica), as well as insulin (Sorin Biomedica) and C-peptide (Mallinckrodt Diagnostica). Intraassay and interassay coefficients of variation for androstenedione, DHEAS, free testosterone, estradiol, SHBG, insulin, and C-peptide were 4.3% and 6.0%, 3.2% and 8.4%, 4.0% and 3.7%, 5.5% and 9.5%, 4.1% and 7.2%, 10.6% and 10.8%, and 4.3% and 7.0%, respectively.

Statistical Analysis

Data are expressed as the mean ± SE. The three groups were compared by one-way ANOVA with multiple comparison testing. Statistical analysis included Pearson correlation coefficients, partial correlation coefficients, and multiple linear regression. Forward stepwise multiple linear regression was used. Because some of the independent variables were highly correlated, thereby raising concerns about multicolinearity, we also performed the multiple linear regression analysis using backward elimination. The latter analysis yielded results similar to those obtained with a forward stepwise method. Age, smoking, duration of obesity, BMI, WHR, and sex hormones were the independent variables. For each variable in the final model, standardized β coefficients and significance are given. The overall R^2 may be interpreted as the proportion of overall variability in the dependent variable that is explained by the model, and is presented in an adjusted form to allow comparison between models that include different numbers of explanatory variables. All analyses were performed using the Statistical Package for the Social Sciences software. Differences were considered to attain significance at P less than .05.

Table 1. Clinical Characteristics of the Study Subjects

Characteristic	Upper-Body Obesity	Lower-Body Obesity	Control Group
No. of subjects	27	22	21
Age (yr)	33.5 ± 8.9	36.0 ± 6.3	32.2 ± 7.0
BMI (kg/m^2)	38.2 ± 5.3‡	35.9 ± 4.3‡	21.8 ± 2.3
IBW (%)	162.3 ± 24.1*	152.7 ± 18.3*	96.4 ± 10.3
WHR	0.89 ± 0.05†§	0.77 ± 0.03	0.75 ± 0.05
Duration of obesity (yr)	14.9 ± 6.2	9.6 ± 6.7	

NOTE. Results are presented as the mean ± SD.
*P < .05, †P < .01, ‡P < .001: v control group.
§P < .001, upper-body v lower-body obesity.

RESULTS

Glucose, Insulin, and C-Peptide Levels

Mean fasting glucose and glucose levels after 60 minutes and 120 minutes did not differ between the three groups. Both fasting and glucose-induced insulin levels were significantly higher in women with upper-body obesity than in both the control group ($P < .001$) and those with lower-body obesity ($P < .01$). The cumulative insulin response tended to be higher in women with upper-body obesity than in the other two groups ($P < .001$ for each). Mean fasting and glucose-induced insulin levels did not differ significantly in the lower-body obesity group compared with the control group (Fig 1 and Table 2).

Mean fasting C-peptide concentrations were significantly higher in both obese groups ($P < .001$ for women with upper-body obesity and $P < .05$ for women with lower-body obesity) than in the control group. However, glucose-induced C-peptide levels were significantly higher in abdominally obese women compared with both the control group ($P < .001$) and women with lower-body obesity ($P < .001$).

Insulin clearance was estimated from the C-peptide to insulin ratio and FEI at time 0. C-peptide to insulin ratios were similar in all three groups (data not shown), and FEI was significantly lower in abdominally obese women than in the control group ($P < .05$).

Sex Hormones and SHBG

Free testosterone serum concentrations were higher in abdominally obese women than in both the controls and women with lower-body obesity ($P < .05$ for each). SHBG serum concentrations were significantly lower in women with upper-body obesity than in the control group ($P < .001$). Androstenedione, DHEAS, and estradiol did not differ significantly between the three groups (Table 3).

Relationships Between Insulin and Sex Hormones

Table 4 shows Pearson correlation coefficients between BMI, WHR, and insulin and sex hormones. Free testosterone serum levels were significantly positively correlated with fasting insulin levels ($r = .362$, $P < .01$). The DHEAS to free testosterone ratio and SHBG were significantly negatively correlated with fasting insulin levels ($r = -.416$, $P < .001$ and $r = -.449$, $P < .001$, respectively). Similar correlations were found between free testosterone, DHEAS to free testosterone ratio, and SHBG and the cumulative insulin response.

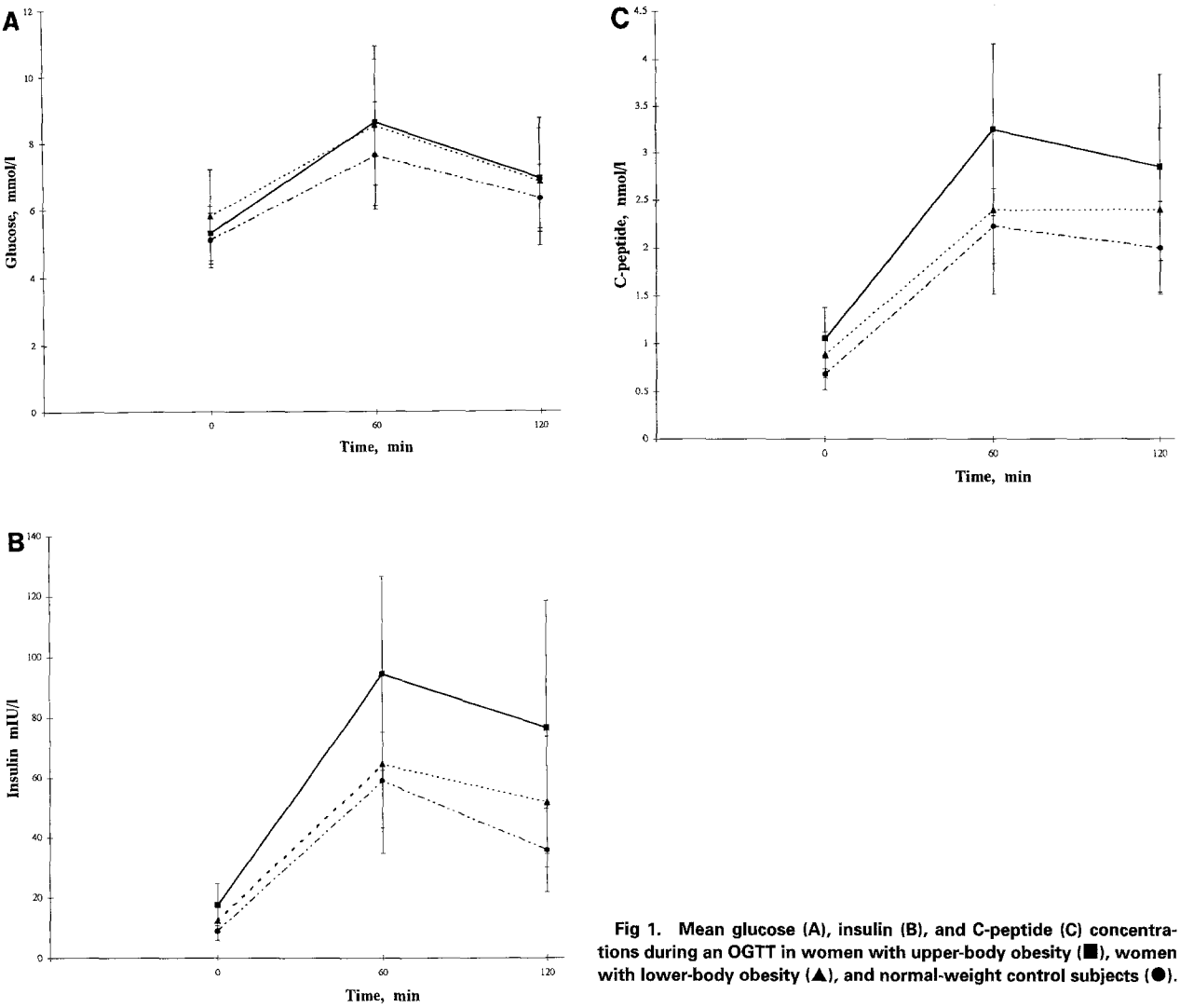

Fig 1. Mean glucose (A), insulin (B), and C-peptide (C) concentrations during an OGTT in women with upper-body obesity (■), women with lower-body obesity (▲), and normal-weight control subjects (●).

After adjustment for WHR, fasting insulin remained positively correlated with free testosterone and negatively correlated with SHBG and the DHEAS to free testosterone ratio.

The relationship between BMI and SHBG remained significant after adjusting for androgen levels (free testosterone and DHEAS to free testosterone ratio), WHR, and insulin levels (both fasting and 2-hour insulin and the cumulative insulin response).

The relationship between WHR and SHBG also remained significant after adjusting for androgen levels (free testosterone and DHEAS to free testosterone ratio) and BMI. However, the relationship between WHR and SHBG was no longer significant after adjusting for the insulin response.

The relationship between insulin (both fasting and 2-hour insulin and the cumulative insulin response) and SHBG levels remained significant after adjusting for androgens (free testosterone and DHEAS to free testosterone ratio) and WHR. After adjustment for BMI, fasting insulin concentrations were no longer significantly correlated with SHBG. However, both the 2-hour insulin level and the cumulative insulin response remained significantly correlated with SHBG levels after adjusting for BMI.

Table 2. Glucose, Insulin, and C-Peptide Concentrations at 0, 60, and 120 Minutes During an OGTT

Parameter	Upper-Body Obesity	Lower-Body Obesity	Control Group
Glucose (mmol/L)			
0 min	5.3 ± 0.8	5.8 ± 1.4	5.1 ± 0.8
60 min	8.6 ± 1.9	8.5 ± 2.4	7.6 ± 1.6
120 min	6.9 ± 1.5	6.8 ± 1.9	6.3 ± 1.0
Glucose area (h · mmol/L)	14.7 ± 2.3	14.8 ± 3.7	13.3 ± 2.1
Insulin (mIU/L)			
0 min	17.5 ± 6.9‡§	12.2 ± 4.3	8.8 ± 3.0
60 min	94.3 ± 32.0‡‖	64.4 ± 29.9	59.0 ± 15.9
120 min	76.4 ± 42.0‡§	51.7 ± 21.9	35.7 ± 14.0
Insulin area (h · mIU/L)	141.3 ± 45.1‡‖	96.4 ± 40.0	71.2 ± 22.3
C-peptide (nmol/L)			
0 min	1.05 ± 0.32‡	0.88 ± 0.24*	0.68 ± 0.16
60 min	3.24 ± 0.91‡‖	2.39 ± 0.88	2.22 ± 0.39
120 min	2.84 ± 0.98†	2.39 ± 0.86	1.99 ± 0.48
C-peptide area (h · nmol/L)	5.18 ± 1.39‡§	4.03 ± 1.33	3.56 ± 0.63

NOTE. Results are expressed as the mean ± SD.
*$P < .05$, †$P < .01$, ‡$P < .001$: *v* control group.
§$P < .01$, ‖$P < .001$: upper-body *v* lower-body obesity.

Table 3. Serum Sex Hormone Concentrations

Hormone	Upper-Body Obesity	Lower-Body Obesity	Control Group
Free testosterone (pmol/L)	8.3 ± 3.7*§	5.6 ± 2.8	5.6 ± 2.7
Androstenedione (ng/mL)	2.3 ± 1.1	1.8 ± 0.7	2.3 ± 0.9
DHEAS (μmol/L)	5.1 ± 2.4	4.9 ± 2.3	4.9 ± 1.9
DHEAS/free testosterone	0.71 ± 0.39	1.04 ± 0.56	1.05 ± 0.52
Estradiol (pmol/L)	226.8 ± 95.7	234.4 ± 116.4	173.4 ± 96.2
SHBG (nmol/L)	24.0 ± 10.2‡	31.1 ± 8.5†	45.3 ± 15.4

NOTE. Results are expressed as the mean ± SD.
*$P < .05$, †$P < .01$, ‡$P < .001$: *v* control group.
§$P < .05$, upper-body *v* lower-body obesity.

Since sex hormones have complex precursor-product relationships with each other, multivariate regression analysis was performed in an attempt to adjust statistically for such effects (Tables 5 and 6).

In the first set of models (Table 5), fasting insulin, 2-hour insulin, and the cumulative insulin response were independent variables and age, smoking, BMI, WHR, duration of obesity, androgens, estradiol, and SHBG were independent variables. BMI ($P < .01$) and the ratio of DHEAS to free testosterone ($P < .01$) had the strongest association with fasting insulin. WHR had a strong independent association with the insulin response ($P < .0005$), as well as the duration of obesity ($P < .01$) and the androstenedione level ($P < .01$). Similarly, the duration of obesity ($P < .01$), WHR ($P < .05$), and androstenedione level ($P < .05$) had an independent association with 2-hour insulin concentrations.

In the second set of models, we reversed dependent and independent variables (Table 6). Fasting insulin had the strongest association with the ratio of DHEAS to free testosterone ($P < .0005$). Age ($P < .0005$), duration of obesity ($P < .01$), and fasting insulin ($P < .05$) had an independent association with free testosterone. Age ($P < .0005$) and the 2-hour insulin level ($P < .01$) had a strong association with androstenedione.

DISCUSSION

The results of our study in healthy premenopausal women with a normal menstrual cycle and no hirsutism indicate that healthy obese premenopausal women with a high WHR are characterized by elevated fasting and glucose-induced insulin levels and hyperandrogenism as indicated by elevated free testosterone serum concentrations and low SHBG levels. We found that our abdominally obese premenopausal women were insulin-resistant, as evident from their twofold higher fasting and glucose-induced insulin concentrations. In subjects with normal and abnormal glucose tolerance, fasting insulin was the best marker of insulin resistance as determined by whole-body glucose uptake using the euglycemic-hyperinsulinemic clamp technique.[21] The 2-hour insulin concentration during the OGTT was a reliable marker of insulin resistance for subjects with normal glucose tolerance, but not for those with abnormal glucose tolerance. In recent studies, the 30-minute insulin concentration and 30-minute insulin increment during an OGTT has been shown to be a good marker of insulin secretion.[22,23]

The question arises as to whether enhanced postload insulin levels represent a truly increased insulin secretion or whether a

Table 4. Correlation Coefficients Between Anthropometric Measures, Sex Hormones and Metabolic Indices

Parameter	BMI	WHR	Insulin 0 h	Insulin 2 h	Insulin Area
Free testosterone	.270	.179	.362*	.345*	.297*
Androstenedione	−.067	.008	.125	.281*	.228
DHEAS	−.045	−.044	−.098	−.019	−.108
DHEAS/free testosterone	−.290*	−.215	−.416†	−.293†	−.336†
Estradiol	.109	.124	−.017	.138	.152
SHBG	−.622†	−.445†	−.449†	−.497†	−.505†
BMI	1.000	.549	.587†	.439†	.548†
WHR	.549†	1.000	.419†	.488†	.599†

*$P < .01$.
†$P < .001$.

Table 5. Multiple Regression Analysis of Variables Modifying Fasting Insulin Levels and the Insulin Response

Independent Variables	Dependent Variables: Insulin 0 h	Insulin 2 h	Insulin Area
Age	−.059	−.059	−.056
Smoking	.057	−.039	−.063
BMI	.509†	.088	.173
WHR	.118	.247*	.389‡
Duration of obesity	−.026	.397†	.363†
Free testosterone	.087	.076	.022
Androsteredione	.083	.312*	.255†
DHEAS/free testosterone	−.268†	−.059	−.107
SHBG	−.071	−.196	−.153
Estradiol	−.101	−.064	.024
R^2	.343	.383	.474

NOTE. Results are standardized β coefficients and significance, and adjusted R^2 for each model.
*$P < .05$.
†$P < .01$.
‡$P < .0005$.

Table 6. Multiple Regression Analysis of Variables Modifying Sex Hormone Serum Concentrations

Independent Variables	Dependent Variables: Free Testosterone	DHEAS/Free Testosterone	Androstenedione
Age	−.598‡	.185	−.489‡
Smoking	.143	−.105	−.057
Duration of obesity	.287†	−.101	−.142
BMI	.120	−.142	−.100
WHR	.128	−.121	.020
Insulin 0 h	.233*	−.418‡	.032
Insulin 2 h	.090	−.076	.270†
Insulin area	.004	−.114	.076
R^2	.432	.183	.256

NOTE. Results are standardized β coefficients and significance, and adjusted R^2 for each model.
*$P < .05$.
†$P < .01$.
‡$P < .0005$.

decreased insulin clearance contributes. It appears well established that obesity in general is associated with both increased insulin production and decreased insulin clearance.[20,24] The pancreas secretes insulin and C-peptide in equimolar amounts, and hepatic extraction of C-peptide is negligible. Therefore, it is generally accepted that the C-peptide level represents an appropriate measure of insulin production, and either the C-peptide to insulin ratio or FEI represents insulin clearance. In our subjects, both obese groups and healthy controls had a similar C-peptide to insulin ratio, but FEI was significantly decreased only in women with upper-body obesity. Our results might indicate that in abdominal adiposity decreased hepatic extraction of insulin contributes to basal hyperinsulinemia. These results confirm the findings of previous studies of obese hyperandrogenic women.[25,26] In a recent study, Buffington and Kitabchi[26] found that the hyperinsulinemia of hyperandrogenic PCO women may occur from diminished insulin clearance and defects in peripheral insulin degradation. Peiris et al[24] found in non-PCO premenopausal women that insulin production was positively correlated with total body mass, and insulin clearance was a correlate of the amount of abdominal obesity alone. Thus, decreased hepatic insulin clearance and increased splanchnic insulin levels might account for the decreased hepatic SHBG production. However, it seems likely that a major portion of the increased insulin response is due to increased insulin production, which presumably could be an expression of enhanced sensitivity to glucose or increased β-cell mass.[27]

The aim of our study was to identify the strongest statistical determinants of insulin levels among anthropometric variables and sex hormones. We found the fasting insulin, glucose-induced insulin, and cumulative insulin response of all our subjects to be correlated positively with free testosterone and negatively with the DHEAS to free testosterone ratio and SHBG. These results confirm the findings of previous studies.[13,28,29]

The relationship between SHBG and insulin was independent of the degree of obesity, obesity type, and androgen status. The significant reduction in the strength of the association between WHR and SHBG after adjusting for insulin suggests that the hyperinsulinemia that accompanies increasing adiposity may play an important role in the diminished SHBG level. Nestler et al[30] have documented that hyperinsulinemia can directly reduce SHBG levels in obese women with PCO. There is an increasing body of evidence suggesting that elevated insulin levels in insulin-resistant states directly enhance ovarian androgen production and suppress hepatic SHBG production.[14,31,32] However, some investigators provide evidence that hyperandrogensim can induce insulin resistance.[15]

Abdominal obesity, hyperandrogenism, and insulin resistance are highly interrelated. Among potential confounding variables (age, smoking, anthropometric variables, and sex hormones), the most important independent determinants of fasting insulin levels were BMI and the DHEAS to free testosterone ratio. All parameters of insulin sensitivity were more strongly correlated with the ratio of DHEAS to free testosterone than with either DHEAS or free testosterone alone. In previous studies in women with PCO, a negative correlation between DHEAS and insulin has been observed, with testosterone exhibiting the opposite trend.[28,33,34] Ovesen et al[35] recently failed to show changes in insulin action in lean hyperandrogenic women, suggesting that relatively high DHEAS levels may increase insulin sensitivity. Buffington et al,[28] from in vivo and in vitro studies of obese hyperandrogenic women with marked insulin resistance, suggested that DHEAS and testosterone may have opposing actions on insulin sensitivity. The results of our study, contrary to the other that investigated hyperandrogenic PCO women, provide further evidence suggesting that DHEAS and free testosterone may have opposing effects on insulin action, and that the ratio of DHEAS to free testosterone may be an important determinant of insulin sensitivity in healthy nonhirsute women, as it proposed previously for hyperandrogenemic women. Therefore, our results extend the prior findings on the negative correlation between the DHEAS to testosterone ratio and insulin level from Buffington et al[28] to the female population in general.

The WHR, duration of obesity, and androstenedione level had a strong independent association with the 2-hour insulin serum concentration and cumulative insulin response. Obesity is one of the most important risk factors for NIDDM. However, it is not known whether the duration of obesity influences the incidence of diabetes independently of the current degree of obesity. A few studies have been published on the effects of the duration of obesity on the incidence of NIDDM, but only one has had adequate measures of the duration of obesity.[36,37] Everhard et al[37] have reported that the duration of obesity was a significant risk factor for NIDDM independently of the degree of obesity. However, they found that fasting insulin and 2-hour insulin concentrations were inversely associated with the duration of obesity. In our study, the duration of obesity was determined as the time when significant obesity occurred, but measures of the duration of obesity have not been adequate because of a potentially large subjective element. Although it is a limitation of our study, these results suggest that in healthy women with normal glucose tolerance the duration of obesity enhances glucose-induced insulin levels and the cumulative insulin response independently of the degree of obesity and obesity type. Resistance to glucose disposal is strongly associated with obesity and results in high fasting and glucose-induced insulin concentrations. A prolonged duration of obesity could markedly worsen this resistance and result in even higher insulin concentrations. Thus, the role of the duration of obesity in future studies should be considered.

The WHR had a strong independent association with the cumulative insulin response. The WHR is strongly related to intraabdominal fat mass, which is in turn more closely correlated with glucose and insulin levels than the subcutaneous fat mass.[38,39] Recent studies have shown that intraabdominal adipocytes have a higher sensitivity to the stimulation of lipid mobilization processes and that the antilipolytic effect of insulin on these cells is less than on subcutaneous adipocytes.[40]

Among potential confounding factors (age, smoking, anthropometric variables, and sex hormones), the degree of obesity and the ratio of DHEAS to free testosterone appeared to have the strongest effect on fasting insulin levels, and the WHR, duration of obesity, and androstenedione level appeared to have the strongest effect on the 2-hour insulin level and the cumulative insulin response.

In conclusion, in large number of healthy premenopausal

women without clinical signs of hyperandrogenism, increased BMI and more pronounced upper-body fat localization resulted in hyperinsulinemia and hyperandrogenism, as evident by significantly elevated free testosterone serum levels and low SHBG concentrations. The duration of obesity exaggerated glucose-induced insulin levels and the cumulative insulin response independently of the degree of obesity and obesity type. The ratio of DHEAS to free testosterone was an independent determinant of fasting insulin concentrations. Furthermore, the ratio of DHEAS to free testosterone rather than either of these androgens alone may be important in the regulation of insulin action in females.

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