0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(1):310–315

doi: 10.1210/jc.2004-1006

β-Cell Function: A Key Pathological Determinant in Polycystic Ovary Syndrome

Mark O. Goodarzi, Stephen Erickson, Sidney C. Port, Robert I. Jennrich, and Stanley G. Korenman

Division of Endocrinology, Diabetes, and Hypertension (M.O.G., S.G.K.), Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California 90095; Division of Endocrinology, Diabetes, and Metabolism and Department of Obstetrics and Gynecology (M.O.G.), Cedars-Sinai Medical Center, Los Angeles, California 90048; and Department of Statistics (S.E., S.C.P., R.I.J.), University of California, Los Angeles, Los Angeles, California 90095

We report data from 60 patients with polycystic ovary syndrome (PCOS) who had undergone assessment of insulin resistance, pancreatic β-cell function, obesity, and androgen levels to elucidate the complex relationships among these traits. Homeostasis model assessment was used to quantify insulin resistance and β-cell function. A reference population was derived from the National Health and Nutrition Examination Study (NHANES III, 1988–1994). Indices of insulin resistance, insulin secretion, bioavailable testosterone, and body mass index all exhibited significant pairwise correlations. Multiple regression analysis clarified the phenotypic relationships, demonstrating that insulin resistance and bioavailable testosterone were independent predictors of β-cell function; β-cell function and obesity were independent predictors of insulin resistance; and β-cell function was an independent predictor of bioavailable testosterone. Of note, comparison with normal women from NHANES revealed a significantly stronger relationship between β-cell function and insulin resistance in PCOS, raising the possibility of an intrinsic defect in β-cell function whereby increasing insulin resistance leads to a greater insulin response in PCOS than normal. The altered relationship of β-cell function and insulin resistance coupled with the fact that β-cell function, not insulin resistance, was a predictor of hyperandrogenemia suggests that β-cell dysfunction may be a key pathogenic determinant in PCOS. (*J Clin Endocrinol Metab* 90: 310–315, 2005)

POLYCYSTIC OVARY SYNDROME (PCOS) is found in 4–7% of women of reproductive age, making it the most common endocrine disorder in women (1, 2). For many years, obesity has been an important feature of the syndrome. More recently, investigators recognized insulin resistance, which characterizes 50–90% of PCOS women (3–5), as a central component of PCOS, possibly playing an underlying pathogenic role (6). PCOS, in turn, may confer a risk of insulin resistance in addition to that caused by obesity (7, 8). However, it is not clear whether insulin resistance itself or the resultant compensatory hyperinsulinemia leads to the hormonal abnormalities in PCOS. Of the handful of studies that address insulin secretion in PCOS, some describe increased insulin secretion (9–16), although others suggest decreased insulin secretion (17–19).

For these reasons we sought to better understand the role of pancreatic insulin secretion in PCOS, in particular to place it in the context of insulin resistance, hyperandrogenemia, and obesity. To achieve this goal, we analyzed a cohort of PCOS patients who had undergone detailed characterization of these phenotypes and compared it with a matched normal population. Simple correlation and multiple regression analyses were used to describe the relationships among these traits. We found an altered relationship between β-cell function and insulin resistance in PCOS compared with normal women.

Subjects and Methods

We conducted an Institutional Review Board-approved retrospective chart review of patients presenting to S.G.K.'s university-based (David Geffen School of Medicine at UCLA) reproductive endocrinology clinic with chief complaints of hirsutism, alopecia, acne, or weight gain. Criteria defining PCOS were those of the 1990 National Institute of Child Health and Human Development Consensus Conference (20), namely that there was evidence of hyperandrogenism and oligo-ovulation with exclusion of other disorders known to result in a hyperandrogenic syndrome, such as Cushing's disease or congenital adrenal hyperplasia. Hyperandrogenism was either clinical in the form of hirsutism, acne, or alopecia, or biochemical in the form of an elevated serum androgen level. Clinical assessment was made by the same physician in all cases. Oligo-ovulation was considered to be present if the patient gave a history of a reduced frequency of menses (missed periods or secondary amenorrhea) or if anovulation was demonstrated by luteal phase progesterone measurement.

Exclusion criteria included a hyperandrogenic disorder other than PCOS, such as Cushing's syndrome, 21-hydroxylase deficiency, or hyperandrogenic insulin resistance acanthosis nigricans syndrome. 21-Hydroxylase deficiency presenting as adult-onset (nonclassical) adrenal hyperplasia was diagnosed using standard criteria (21, 22). Also excluded were patients who at presentation were receiving medications that could alter the endocrine and metabolic parameters under investigation, because we wanted to characterize PCOS as it affects women before treatment. Such medications included oral contraceptives, metformin, glucocorticoids, and dexamethasone. Patients were also excluded if they had impaired fasting glucose, diabetes mellitus, anorexia nervosa, hypopituitarism, prolactinoma, or active thyroid disease, with the latter assessed by prolactin and TSH measurements. Hypopituitarism was excluded biochemically when a suggestive history or physical exam findings were present. In light of the above entry and exclusion

First Published Online October 26, 2004

Abbreviations: BMI, Body mass index; HOMA, homeostasis model assessment; HOMA-IR, index of insulin resistance; HOMA-%B, index of β-cell function; NHANES, National Health and Nutrition Examination Study; PCOS, polycystic ovary syndrome; SHBG, sex-hormone-binding globulin; SRC, standardized regression coefficient.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

criteria, 60 cases of PCOS (of 143 charts reviewed) were deemed appropriate for inclusion in this study.

Anthropometric and laboratory data were always measured during initial evaluation, before institution of therapy. A clinic nurse obtained the weight, height, and blood pressure of each subject. Age was determined at time of presentation. Body mass index (BMI) was calculated as kg/m^2. All 60 had a morning fasting glucose, insulin, and total and bioavailable [non-sex-hormone-binding globulin (non-SHBG)-bound] testosterone, as previously described (23). The laboratory performing the blood tests (Quest Diagnostics, San Juan Capistrano, CA, for hormonal measurements) provided normal values; all other tests were done at the University of California, Los Angeles, Clinical Laboratory.

The homeostasis model assessment (HOMA) was used to calculate indices of insulin resistance and insulin secretion for each patient (24, 25). The computer-based HOMA calculator (available at www.dtu.ox.ac.uk/homa) uses fasting glucose and insulin to generate the index of insulin resistance, HOMA-IR, and the index of β-cell function, HOMA-%B. An ideal, normal-weight person less than 35 yr of age has a HOMA-IR of 1 and HOMA-%B of 100% (26).

Data from the National Health and Nutrition Examination Study (NHANES III) (27) were used to obtain a population of normal women for comparison with women with PCOS. Subjects from NHANES III who had glucose and insulin levels obtained after at least 8 h fasting were selected to match the age, BMI, and racial/ethnic distribution of the PCOS group. Thus, the groups were comparable in age (NHANES mean age, 27.8 yr with a range of 15–39 yr; PCOS mean age, 26.2 yr with a range of 13–46 yr) and BMI (NHANES mean BMI, 30.0 kg/m^2 with a range of 24–69 kg/m^2; PCOS mean BMI, 30.6 kg/m^2 with a range of 19–64 kg/m^2). Both populations had equal proportions of Caucasian subjects (64%), Mexican-Americans (11%), African-Americans (9%), and other ethnic groups (16%). We excluded participants who were using insulin or who had a fasting glucose greater than 110 mg/dl (6.1 mmol/liter) or a glycosylated hemoglobin greater than 6% to remove individuals with glucose intolerance or diabetes, yielding 486 subjects for analysis. The methods used for glucose, insulin, and lipid levels are detailed in the NHANES report (27).

Statistical analysis

Parameters that had a skewed distribution (weight, BMI, insulin, HOMA-IR, HOMA-%B, and total and bioavailable testosterone values) were log transformed for all analyses to reduce skewness. Henceforth reference to these variables will always mean their log-transformed values. Student's *t* test was used to compare means between PCOS and NHANES. A P value < 0.05 was considered statistically significant. Simple correlation analyses were carried out comparing all possible pairwise combinations of the variables HOMA-%B, HOMA-IR, age, BMI, bioavailable testosterone, and total testosterone for both the PCOS and NHANES populations (testosterone was not measured in NHANES). A large sample test (28) was used to compare corresponding correlation coefficients between the two populations. In the PCOS group, multiple regression analysis was conducted 1) with HOMA-IR, age, BMI, and bioavailable testosterone as independent variables and HOMA-%B as the dependent variable; 2) with HOMA-%B, age, BMI, and bioavailable testosterone as independent variables and HOMA-IR as the dependent variable; and 3) with HOMA-IR, HOMA-%B, age, and BMI as independent variables and bioavailable testosterone as the dependent variable. Analyses were conducted using Statview 5.01 and SAS software (SAS Institute, Cary, NC).

Results

Phenotypic correlations in PCOS

The phenotypic correlations among insulin resistance, β-cell function, testosterone levels, age, and BMI, assessed by pairwise correlations, are displayed in Table 1. HOMA-IR values indicated a wide range of insulin resistance from 0.35–6.9. HOMA-%B values ranged from 58–382%, indicating a broad range of insulin secretion. The highly significant correlation ($r = 0.91$; $P < 0.0001$) between HOMA-IR and HOMA-%B indicated increasing (compensatory) insulin secretion with increasing insulin resistance.

Obesity is known to correlate with insulin resistance. As predicted, in PCOS, there was a significant correlation between BMI and HOMA-IR ($r = 0.57$; $P < 0.0001$). BMI was also correlated with HOMA-%B ($r = 0.50$; $P = 0.0002$), but age was not significantly correlated with HOMA-IR ($r = -0.13$; $P = 0.32$) or HOMA-%B ($r = -0.19$; $P = 0.16$).

Total and bioavailable testosterone values were available for the PCOS group only. Total testosterone was not significantly correlated with insulin resistance, insulin secretion, age, or BMI. However, bioavailable testosterone was correlated with fasting insulin ($r = 0.44$; $P = 0.0005$), with HOMA-IR ($r = 0.42$; $P = 0.0016$), and with HOMA-%B ($r = 0.49$; $P = 0.0002$). Bioavailable testosterone was also correlated with BMI ($r = 0.33$; $P = 0.016$).

Given the complex of interrelationships among insulin-related traits, hyperandrogenemia, and body mass, we next used multiple regression analyses to elucidate the most important independent predictors of insulin resistance, β-cell function, and bioavailable testosterone.

Independent factors influencing β-cell function, insulin resistance, and bioavailable testosterone in PCOS

Table 2 displays the results of analyses that employed HOMA-%B, HOMA-IR, and bioavailable testosterone as dependent variables in separate multiple regressions. In women with PCOS, regression of age, BMI, HOMA-IR, and bioavailable testosterone on HOMA-%B showed that age and BMI were not significant predictors of HOMA-%B ($P = 0.33$ and 0.71). The strongest predictor of HOMA-%B as judged by standardized regression coefficients (SRC) was HOMA-IR ($SRC = 0.86$; $P < 0.0001$), followed by bioavailable testosterone ($SRC = 0.15$; $P = 0.023$).

Multiple regression of HOMA-IR on age, BMI, HOMA-%B, and bioavailable testosterone revealed that the most important predictors of insulin resistance (HOMA-IR) were BMI ($SRC = 0.15$; $P = 0.033$) and HOMA-%B ($SRC = 0.88$;

TABLE 1. Correlation among phenotypes in women with PCOS

	HOMA-%B	HOMA-IR	BMI	Age	Total testosterone	Bioavailable testosterone
HOMA-%B	—	**0.91**	**0.50**	−0.19	−0.045	**0.49**
HOMA-IR	<0.0001	—	**0.57**	−0.13	−0.19	**0.42**
BMI	0.0002	<0.0001	—	0.19	−0.049	**0.33**
Age	0.16	0.32	0.18	—	−0.029	−0.14
Total testosterone	0.74	0.17	0.73	0.82	—	**0.48**
Bioavailable testosterone	0.0002	0.0016	0.016	0.28	0.0001	—

Correlation coefficients are above the diagonal; *P* values for each pairwise correlation are below the diagonal. Significant correlation coefficients are indicated in *bold*.

TABLE 2. Multiple regression analyses in women with PCOS

	HOMA-%B		HOMA-IR		Bioavailable testosterone		Age		BMI	
	RC (SRC)	*P* value	RC (SRC)	*P* value	RC (SRC)	*P* value	RC (SRC)	*P* value	RC (SRC)	*P* value
HOMA-%B	NA	NA	**0.53 (0.86)**	<0.0001	**0.094 (0.15)**	0.023	−0.002 (−0.06)	0.33	−0.045 (−0.027)	0.71
HOMA-IR	**1.43 (0.88)**	<0.0001	NA	NA	−0.078 (−0.077)	0.26	0.001 (0.017)	0.78	**0.41 (0.15)**	0.033
BT	**1.18 (0.74)**	0.023	−0.36 (−0.37)	0.26	NA	NA	−0.006 (−0.12)	0.36	0.34 (0.13)	0.41

The SRC allows direct comparison, within a given patient group, of the magnitude of the effects of the independent variables on the dependent variable. Significant correlation coefficients are indicated in *bold*. BT, Bioavailable testosterone; NA, not applicable; RC, regression coefficient.

$P < 0.0001$). In contrast to β-cell function, bioavailable testosterone was not a significant predictor of HOMA-IR in this analysis.

HOMA-IR and HOMA-%B, as well as age and BMI, were examined as independent predictors of bioavailable testosterone. In this analysis, the only independent predictor of bioavailable testosterone was HOMA-%B (SRC = 0.74; P = 0.023).

Insulin resistance and β-cell function: PCOS vs. normal women

Anthropometric and metabolic characteristics of the PCOS patients and the age-, BMI-, and ethnicity-matched normal women from NHANES are presented in Table 3. Average levels of fasting glucose and insulin-related traits did not differ significantly between the two groups.

In the NHANES group, all of the correlation coefficients were highly significant because of the large sample size (Table 4). The simple correlation between BMI and HOMA-IR ($r = 0.47$; $P < 0.0001$) was similar to that observed in PCOS ($P = 0.34$ for comparison of coefficients). In NHANES, the simple correlation between HOMA-IR and HOMA-%B ($r = 0.77$; $P < 0.0001$) gave a smaller coefficient than that observed in PCOS. A small but statistically significant correlation existed between age and HOMA-%B ($r = -0.23$; $P < 0.0001$), and age and HOMA-IR were marginally correlated ($r = -0.1$; $P = 0.049$).

The observed differences in correlation coefficients between women with PCOS and normal women led us to ask whether the relationship between HOMA-%B and HOMA-IR was different between the two groups. A large sample test showed there was a significant difference in the correlation of HOMA-%B to HOMA-IR between PCOS and NHANES ($P = 0.0076$) with the correlation in PCOS being considerably stronger (0.91 *vs.* 0.77). To illustrate the differential relationship of HOMA-%B and HOMA-IR, Fig. 1 presents overlaid regression plots for HOMA-%B *vs.* HOMA-IR for PCOS and NHANES. These plots depict the effect of incremental increases in HOMA-IR on HOMA-%B. The greater effect of HOMA-IR on HOMA-%B in PCOS is reflected in the steeper slope of the regression line for PCOS (Fig. 1), indicating that a given increase in HOMA-IR results in a larger increment in HOMA-%B in women with PCOS than in those without.

Discussion

This study aimed to characterize the most important independent determinants of β-cell function, insulin resistance, and hyperandrogenemia in PCOS. Although all pairwise correlations of HOMA-%B, HOMA-IR, and bioavailable testosterone were statistically significant, multiple regression analyses allowed identification of the most significant predictors of each trait. Our study was unique in that we compared inter-trait correlations between PCOS and normal women, not simply mean values. This approach demonstrated a disproportionate elevation of β-cell function compared with insulin resistance in PCOS compared with normal women, a dramatic finding given that the two groups had similar mean values of these insulin-related traits.

The use of women from NHANES provided a very large normal control group; even if 5% of this population had PCOS it would not have altered the results. In fact, the presence of PCOS in the NHANES population would tend to hinder detection of differences in a comparison of our PCOS patients with NHANES. Direct comparison of mean trait values, as in Table 3, must be interpreted with some caution because the glucose and insulin determinations were made in different laboratories.

The unsuspected importance of β-cell function

In PCOS and normal women, the most significant predictor of β-cell function was insulin resistance. This is consistent with the concept of compensatory insulin hypersecretion in response to insulin resistance. Compensatory hyperinsulinemia serves to maintain normal plasma glucose levels in the face of insulin resistance. Because the patients were selected to have normal fasting glucose levels (range, 69–105 mg/dl or 3.8–5.8 mmol/liter), they had adequate β-cell function. The most insulin-resistant patients with PCOS in this study had β-cells secreting insulin at very high levels. These patients may be at increased risk of β-cell exhaustion and development of type 2 diabetes mellitus (29).

TABLE 3. Anthropometric and metabolic comparison of women with PCOS and normal women

	Age (yr)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Glucose (mg/dl)	Fasting insulin (μIU/ml)	HOMA-IR	HOMA-%B (%)
PCOS (n = 60)	26.2 ± 6.5	164.5 ± 8.1	83.5 ± 26.9	30.6 ± 9.9	89.1 ± 9.0	15.5 ± 13.4	1.87 ± 1.58	140.8 ± 74.9
NHANES (n = 486)	27.8 ± 7.0	162.2 ± 6.9	79.0 ± 15.7	30.0 ± 5.6	87.3 ± 8.9	11.8 ± 6.7	1.54 ± 0.85	133.3 ± 44.0
P value[a]	0.10	0.025	0.34	0.72	0.14	0.25	0.74	0.78

To convert glucose from mg/dl to mmol/liter, multiply by 0.05551. To convert insulin from μIU/ml to pmol/liter, multiply by 7.175.
[a] PCOS *vs.* normal women.

TABLE 4. Correlation among phenotypes in normal women

	HOMA-%B	HOMA-IR	BMI	Age
HOMA-%B	—	**0.77**	**0.40**	**−0.23**
HOMA-IR	<0.0001	—	**0.47**	**−0.10**
BMI	<0.0001	<0.0001	—	**0.091**
Age	<0.0001	0.049	0.045	—

Correlation coefficients (R) are *above the diagonal; P* values for each pairwise correlation are *below the diagonal*. Significant correlation coefficients are indicated in *bold*.

In contrast to insulin resistance in PCOS, there have been comparatively few studies examining β-cell function/insulin secretion in PCOS. Several studies demonstrated increased insulin secretion in PCOS compared with normal (9–16), although other studies demonstrated decreased insulin secretion in PCOS (17–19). Different results have been observed depending on whether insulin secretion was assessed in the basal *vs.* postabsorptive state (30). Another possible confounding factor is that many studies quantified insulin secretion without accounting for the prevailing level of insulin resistance; this is essential to accurate interpretation of indices of β-cell function because insulin secretion and insulin sensitivity have been shown to have a hyperbolic relationship (31). Insulin secretion may be adjusted for insulin resistance using statistical means or by employing the disposition index, the product of an index of insulin secretion with an index of insulin sensitivity. Nevertheless, even among careful studies making this adjustment, conflicting results regarding insulin secretion in PCOS are found in the literature (14, 18, 32). We avoided this problem by examining the relationship between insulin secretion and insulin resistance, rather than comparing mean values. Although we did not find BMI to be an independent predictor of β-cell function, others have observed differences in β-cell function between lean and obese women with PCOS, with increased insulin secretion in lean PCOS and decreased insulin secretion in obese PCOS (32). Insulin secretion tends to be decreased in women with PCOS and impaired glucose tolerance; a study of obese, insulin-resistant adolescents with PCOS found that those with impaired glucose tolerance or diabetes had impaired β-cell response to the same degree of insulin resistance as the normoglycemic patients (17). In a separate study, normal glucose-tolerant women with PCOS had increased insulin secretion, whereas those with impaired glucose tolerance had decreased insulin secretion (14). Similarly, women with polycystic ovaries and a history of gestational diabetes have impaired β-cell function (33, 34). Thus, the heterogeneity observed in β-cell function in PCOS may reflect its assessment at different stages of the disorder, with increased β-cell function in lean subjects with normal glucose tolerance and decreased β-cell function in obese subjects who have mild (manifesting during pregnancy as gestational diabetes) or overt impairment in glucose tolerance.

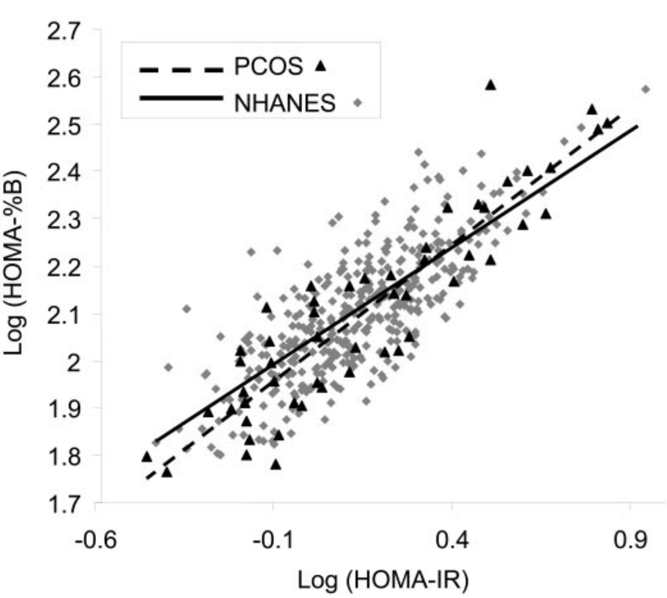

FIG. 1. Regression plot of HOMA-IR on HOMA-%B. The plot is an overlay of the simple regression plots for PCOS and for NHANES.

A key finding in this study was the altered relationship of β-cell function and insulin resistance in PCOS in comparison with normal women. The correlation coefficients relating HOMA-%B to HOMA-IR were higher in PCOS, indicating a greater degree of compensatory insulin secretion for a given increment in insulin resistance. The basis of this difference is unknown. Perhaps in PCOS there is a genetic variant in the pancreatic β-cell that leads to insulin hypersecretion. In fact, in studies of families of women with PCOS, insulin secretion levels, quantified directly by the frequently sampled iv glucose tolerance test, showed significant heritability, suggesting a genetic component to β-cell function in PCOS (35). Higher proinsulin levels in women with PCOS compared with normal have been observed, supporting the hypothesis of altered β-cell function in PCOS (36). Another study observed that weight loss in a group of women with PCOS led to normalization of insulin resistance but did not alter insulin hypersecretion, suggesting that the latter is a primary, intrinsic factor in PCOS (16). Given that HOMA-%B was a significant predictor of bioavailable testosterone in PCOS, it is possible that the tendency to insulin hypersecretion leads to elevated levels of insulin that then contribute to hyperandrogenemia. Indeed, much experimental evidence exists to suggest that insulin has the ability to stimulate ovarian testosterone production (37–39). Whether increased insulin secretion stimulates adrenal androgen hypersecretion is more controversial; however, one study of PCOS women found that during an insulin infusion, adrenal δ-5 androgen output was exaggerated compared with saline infusion, suggesting that hyperinsulinemia potentiated the adrenocortical response to ACTH (40).

The place of insulin resistance

We used HOMA-IR to quantify insulin resistance because this tool has been shown to be a reliable reflection of insulin resistance with a good correlation (r = 0.6–0.88) with the euglycemic hyperinsulinemic glucose clamp study (24, 26, 41). A recent report showed HOMA-IR to have a better correlation with clamp results than even indices derived from oral glucose tolerance tests (42). In women with PCOS and in normal women, HOMA-%B and BMI were significant correlates of HOMA-IR. Whether the insulin resistance often observed in PCOS is because of obesity or an effect of PCOS itself is controversial. Some studies showed similar insulin resistance in weight-matched PCOS and control subjects (19, 43), whereas others demonstrated increased insulin resistance in PCOS compared with weight-matched controls (3, 30, 44). What is widely accepted is that women with both PCOS and obesity have the highest risk for insulin resistance.

In multiple regression analysis in PCOS, BMI was significantly related to HOMA-IR but not to HOMA-%B. This is in agreement with a study wherein weight loss normalized insulin resistance in women with PCOS but did not reduce their increased insulin secretion (16). In another study of lean and obese women with PCOS, insulin resistance was most prominent in the obese subjects, whereas insulin hypersecretion was found in all hyperinsulinemic PCOS patients, regardless of obesity (10). This again highlights the potential importance of pancreatic β-cell function in the pathophysiology of PCOS. If a tendency to insulin hypersecretion is a primary characteristic of PCOS, insulin resistance may yet have importance as a physiological stressor that, by increasing the body's need for insulin, causes the insulin secretory abnormality to become manifest. This is suggested by the greater slope of the HOMA-%B *vs.* HOMA-IR line in PCOS *vs.* normal (Fig. 1).

The role of androgens: bioavailable testosterone

Some studies suggest that insulin resistance/hyperinsulinemia may cause hyperandrogenemia (37–40, 45), whereas others suggest the reverse (46, 47). The current study found a significant correlation between insulin resistance and hyperandrogenemia; however, in multiple regression analysis, the relationship between these traits was insignificant. On the other hand, a robust relationship was found between β-cell function and bioavailable testosterone. As discussed above, this raises the possibility that insulin hypersecretion causes hypersecretion of androgens. Conversely, elevated androgen levels may influence β-cell function, leading to insulin hypersecretion. Consistent with this possibility, a study demonstrating increased insulin secretion in PCOS compared with normal found no difference after adjusting for free androgen index (14). Another alternative is that a common cellular defect leads to both insulin hypersecretion and androgen hypersecretion. Our results demonstrate a significant correlation between HOMA-%B and bioavailable testosterone but do not allow conclusions on causation. What can be inferred is that the correlation of insulin resistance and hyperandrogenemia often observed in PCOS is likely mediated via compensatory insulin hypersecretion.

Bioavailable (non-SHBG-bound) testosterone exhibited significant pairwise correlations with BMI and with HOMA-%B. Although both obesity and hyperinsulinemia may contribute to decreased levels of SHBG, resulting in higher bioavailable testosterone, multiple regression analysis showed that β-cell function had the most direct effect on hyperandrogenemia. It has been suggested that hyperinsulinemia may mediate the decrease in SHBG seen with increasing adiposity (48). Thus, insulin suppression of hepatic synthesis of SHBG (49) may contribute to the correlation of β-cell function and bioavailable testosterone, in addition to a possible effect of insulin on ovarian steroidogenesis (37–39). The fact that total testosterone exhibited no significant inter-trait correlations demonstrates the importance of low SHBG in the hyperandrogenemia of PCOS.

Implications

Insulin resistance is clearly found in many subjects with PCOS and may contribute to increased risk of the metabolic syndrome, development of type 2 diabetes, and cardiovascular disease (6). However, this study demonstrates the under-recognized importance of β-cell function in PCOS. β-Cell function, not insulin resistance, was an important correlate of bioavailable testosterone levels. Women with PCOS demonstrated an altered relationship between insulin resistance and insulin secretion, consistent with an intrinsic β-cell defect wherein insulin resistance leads to an excessive amount of compensatory insulin secretion, with attendant consequences on androgen production and SHBG levels. Insulin hypersecretion may also help to explain the intense hunger experienced by PCOS patients and their ability to gain large amounts of weight in a short period of time. Possibly this insulin hypersecretion was evolutionarily advantageous in times of nutritional deprivation. More research, both at the clinical and cellular levels, is needed to better understand the importance of insulin secretion in PCOS. If β-cell function is indeed a central pathogenic defect in PCOS, therapies that directly modulate insulin secretion may achieve greater success than insulin-sensitizing therapies commonly used today.

Acknowledgments

Received May 26, 2004. Accepted October 18, 2004.

Address all correspondence and requests for reprints to: Mark O. Goodarzi, M.D., Ph.D., Cedars-Sinai Medical Center, Division of Endocrinology, Diabetes, and Metabolism, 8700 Beverly Boulevard, Becker B-128, Los Angeles, California 90048. E-mail: mark.goodarzi@cshs.org.

References

1. **Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S, Escobar-Morreale HF** 2000 A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab 85:2434–2438
2. **Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R** 1998 Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab 83:3078–3082
3. **Dunaif A, Segal KR, Futterweit W, Dobrjansky A** 1989 Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes 38:1165–1174
4. **Dunaif A** 1999 Insulin action in the polycystic ovary syndrome. Endocrinol Metab Clin North Am 28:341–359
5. **Carmina E, Lobo RA** 1999 Polycystic ovary syndrome (PCOS): arguably the most common endocrinopathy is associated with significant morbidity in women. J Clin Endocrinol Metab 84:1897–1899
6. **Goodarzi MO, Korenman SG** 2003 The importance of insulin resistance in polycystic ovary syndrome. Fertil Steril 80:255–258
7. **Dunaif A, Graf M, Mandeli J, Laumas V, Dobrjansky A** 1987 Characterization of groups of hyperandrogenic women with acanthosis nigricans, impaired glucose tolerance, and/or hyperinsulinemia. J Clin Endocrinol Metab 65:499–507
8. **Legro RS, Kunselman AR, Dodson WC, Dunaif A** 1999 Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 84:165–169
9. **Vankova M, Vrbikova J, Hill M, Cinek O, Bendlova B** 2002 Association of insulin gene VNTR polymorphism with polycystic ovary syndrome. Ann NY Acad Sci 967:558–565
10. **Ciampelli M, Fulghesu AM, Cucinelli F, Pavone V, Caruso A, Mancuso S,**

Lanzone A 1997 Heterogeneity in β-cell activity, hepatic insulin clearance and peripheral insulin sensitivity in women with polycystic ovary syndrome. Hum Reprod 12:1897–1901

11. **Ciampelli M, Fulghesu AM, Murgia F, Guido M, Cucinelli F, Apa R, Caruso A, Lanzone A** 1998 Acute insulin response to intravenous glucagon in polycystic ovary syndrome. Hum Reprod 13:847–851
12. **Morales AJ, Laughlin GA, Butzow T, Maheshwari H, Baumann G, Yen SS** 1996 Insulin, somatotropic, and luteinizing hormone axes in lean and obese women with polycystic ovary syndrome: common and distinct features. J Clin Endocrinol Metab 81:2854–2864
13. **Ke WX, Shan GQ, Hua SY** 1996 Different responses of insulin, C-peptide, and testosterone to an oral glucose tolerance test in two groups of women with polycystic ovarian syndrome. Acta Obstet Gynecol Scand 75:166–169
14. **Holte J, Bergh T, Berne C, Berglund L, Lithell H** 1994 Enhanced early insulin response to glucose in relation to insulin resistance in women with polycystic ovary syndrome and normal glucose tolerance. J Clin Endocrinol Metab 78:1052–1058
15. **Tropeano G, Lucisano A, Liberale I, Barini A, Vuolo IP, Martino G, Menini E, Dell'Acqua S** 1994 Insulin, C-peptide, androgens, and β-endorphin response to oral glucose in patients with polycystic ovary syndrome. J Clin Endocrinol Metab 78:305–309
16. **Holte J, Bergh T, Berne C, Wide L, Lithell H** 1995 Restored insulin sensitivity but persistently increased early insulin secretion after weight loss in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 80:2586–2593
17. **Arslanian SA, Lewy VD, Danadian K** 2001 Glucose intolerance in obese adolescents with polycystic ovary syndrome: roles of insulin resistance and β-cell dysfunction and risk of cardiovascular disease. J Clin Endocrinol Metab 86:66–71
18. **Dunaif A, Finegood DT** 1996 β-Cell dysfunction independent of obesity and glucose intolerance in the polycystic ovary syndrome. J Clin Endocrinol Metab 81:942–947
19. **Ehrmann DA, Sturis J, Byrne MM, Karrison T, Rosenfield RL, Polonsky KS** 1995 Insulin secretory defects in polycystic ovary syndrome. Relationship to insulin sensitivity and family history of non-insulin-dependent diabetes mellitus. J Clin Invest 96:520–527
20. **Zawadzki JK, Dunaif A** 1992 Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine F, Merriam GR, eds. Polycystic ovary syndrome. Cambridge, MA: Blackwell Scientific Publications; 377–384
21. **Kiningham RB, Apgar BS, Schwenk TL** 1996 Evaluation of amenorrhea. Am Fam Physician 53:1185–1194
22. **Azziz R, Dewailly D, Owerbach D** 1994 Nonclassic adrenal hyperplasia: current concepts. J Clin Endocrinol Metab 78:810–815
23. **Goodarzi MO, Erickson S, Port SC, Jennrich RI, Korenman SG** 2003 Relative impact of insulin resistance and obesity on cardiovascular risk factors in polycystic ovary syndrome. Metabolism 52:713–719
24. **Wallace TM, Levy JC, Matthews DR** 2004 Use and abuse of HOMA modeling. Diabetes Care 27:1487–1495
25. **Levy JC, Matthews DR, Hermans MP** 1998 Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care 21:2191–2192
26. **Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC** 1985 Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419
27. **Centers for Disease Control and Prevention** 1996 The Third National Health and Nutrition Examination Survey (NHANES III 1988–94) Reference Manuals and Reports [CD-ROM]. Bethesda, MD: National Center for Health Statistics
28. **Jennrich RI** 1970 An asymptotic χ^2 test for the equality of two correlation matrices. J Am Stat Assoc 65:904–912
29. **Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Charles MA, Bennett PH** 1991 A two-step model for development of non-insulin-dependent diabetes. Am J Med 90:229–235
30. **O'Meara NM, Blackman JD, Ehrmann DA, Barnes RB, Jaspan JB, Rosenfield RL, Polonsky KS** 1993 Defects in β-cell function in functional ovarian hyperandrogenism. J Clin Endocrinol Metab 76:1241–1247
31. **Bergman RN, Ader M, Huecking K, Van Citters G** 2002 Accurate assessment of β-cell function: the hyperbolic correction. Diabetes 51(Suppl 1):S212–S220
32. **Vrbikova J, Bendlova B, Hill M, Vankova M, Vondra K, Starka L** 2002 Insulin sensitivity and β-cell function in women with polycystic ovary syndrome. Diabetes Care 25:1217–1222
33. **Holte J, Gennarelli G, Wide L, Lithell H, Berne C** 1998 High prevalence of polycystic ovaries and associated clinical, endocrine, and metabolic features in women with previous gestational diabetes mellitus. J Clin Endocrinol Metab 83:1143–1150
34. **Koivunen RM, Juutinen J, Vauhkonen I, Morin-Papunen LC, Ruokonen A, Tapanainen JS** 2001 Metabolic and steroidogenic alterations related to increased frequency of polycystic ovaries in women with a history of gestational diabetes. J Clin Endocrinol Metab 86:2591–2599
35. **Colilla S, Cox NJ, Ehrmann DA** 2001 Heritability of insulin secretion and insulin action in women with polycystic ovary syndrome and their first degree relatives. J Clin Endocrinol Metab 86:2027–2031
36. **Legro RS, Bentley-Lewis R, Driscoll D, Wang SC, Dunaif A** 2002 Insulin resistance in the sisters of women with polycystic ovary syndrome: association with hyperandrogenemia rather than menstrual irregularity. J Clin Endocrinol Metab 87:2128–2133
37. **Barbieri RL, Makris A, Randall RW, Daniels G, Kistner RW, Ryan KJ** 1986 Insulin stimulates androgen accumulation in incubations of ovarian stroma obtained from women with hyperandrogenism. J Clin Endocrinol Metab 62:904–910
38. **Nestler JE, Jakubowicz DJ, de Vargas AF, Brik C, Quintero N, Medina F** 1998 Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. J Clin Endocrinol Metab 83:2001–2005
39. **Franks S, Gilling-Smith C, Watson H, Willis D** 1999 Insulin action in the normal and polycystic ovary. Endocrinol Metab Clin North Am 28:361–378
40. **Moghetti P, Castello R, Negri C, Tosi F, Spiazzi GG, Brun E, Balducci R, Toscano V, Muggeo M** 1996 Insulin infusion amplifies 17 α-hydroxycorticosteroid intermediates response to adrenocorticotropin in hyperandrogenic women: apparent relative impairment of 17,20-lyase activity. J Clin Endocrinol Metab 81:881–886
41. **Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ** 2000 Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 85:2402–2410
42. **Hanson RL, Pratley RE, Bogardus C, Narayan KM, Roumain JM, Imperatore G, Fagot-Campagna A, Pettitt DJ, Bennett PH, Knowler WC** 2000 Evaluation of simple indices of insulin sensitivity and insulin secretion for use in epidemiologic studies. Am J Epidemiol 151:190–198
43. **Ovesen P, Moller J, Ingerslev HJ, Jorgensen JO, Mengel A, Schmitz O, Alberti KG, Moller N** 1993 Normal basal and insulin-stimulated fuel metabolism in lean women with the polycystic ovary syndrome. J Clin Endocrinol Metab 77:1636–1640
44. **Chang RJ, Nakamura RM, Judd HL, Kaplan SA** 1983 Insulin resistance in nonobese patients with polycystic ovarian disease. J Clin Endocrinol Metab 57:356–359
45. **Taylor SI, Dons RF, Hernandez E, Roth J, Gorden P** 1982 Insulin resistance associated with androgen excess in women with autoantibodies to the insulin receptor. Ann Intern Med 97:851–855
46. **Woodard TL, Burghen GA, Kitabchi AE, Wilimas JA** 1981 Glucose intolerance and insulin resistance in aplastic anemia treated with oxymetholone. J Clin Endocrinol Metab 53:905–908
47. **Moghetti P, Tosi F, Castello R, Magnani CM, Negri C, Brun E, Furlani L, Caputo M, Muggeo M** 1996 The insulin resistance in women with hyperandrogenism is partially reversed by antiandrogen treatment: evidence that androgens impair insulin action in women. J Clin Endocrinol Metab 81:952–960
48. **Peiris AN, Sothmann MS, Aiman EJ, Kissebah AH** 1989 The relationship of insulin to sex hormone-binding globulin: role of adiposity. Fertil Steril 52:69–72
49. **Yki-Jarvinen H, Makimattila S, Utriainen T, Rutanen EM** 1995 Portal insulin concentrations rather than insulin sensitivity regulate serum sex hormone-binding globulin and insulin-like growth factor binding protein 1 *in vivo*. J Clin Endocrinol Metab 80:3227–3232

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.