Relative Impact of Insulin Resistance and Obesity on Cardiovascular Risk Factors in Polycystic Ovary Syndrome

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Polycystic ovary syndrome (PCOS) affects 5% to 7% of women of reproductive age. Insulin resistance and obesity are components of this important syndrome that may contribute to excess cardiovascular risk. We analyzed data from 69 patients with PCOS who had undergone quantitative assessment of insulin sensitivity, blood pressure, lipid profiles, and androgen levels to determine the impact of insulin resistance and obesity on parameters of cardiovascular risk. Homeostasis model assessment (HOMA) was used to stratify patients in terms of insulin resistance. To obtain a reference population, we used data from the National Health and Nutrition Examination Study (NHANES III, 1988 to 1994). The most insulin-resistant tertile of patients exhibited higher body mass index (BMI), androgen levels, systolic and diastolic blood pressure (DBP), triglyceride (TG) levels, and decreased high-density lipoprotein cholesterol (HDL-C) levels. Insulin resistance, not BMI, was the main determinant of HDL-C and TG levels and systolic blood pressure (SBP) in PCOS. Among normal women, both BMI and insulin resistance influenced cardiovascular risk factors. Insulin resistance was a more significant predictor of TGs in women with PCOS than in normal women ($P = .008$). In contrast to normal women, insulin resistance in PCOS appears to be the prime determinant of abnormal lipids, blood pressure, and androgens. Thus, early detection of insulin resistance, as well as weight reduction, should be emphasized for all patients with PCOS.

POLYCYSTIC OVARY SYNDROME (PCOS) is found in 5% to 7% of women of reproductive age, making it the most common endocrine disorder in women.[1] In spite of this, PCOS remains a poorly defined condition. There is no officially accepted set of diagnostic criteria, because women with this disorder present with varying degrees of androgenization, insulin resistance, obesity, menstrual irregularity, and ovarian and/or adrenal androgen excess.[2] PCOS is much more than a disorder of excess hair and anovulation. PCOS has profound implications for self-esteem and mood, interferes with fertility, and is associated with serious complications. About half of women with PCOS are obese.[1] Many features of the cardiovascular dysmetabolic syndrome are observed with increased incidence in women with PCOS, particularly when they reach their fourth and fifth decades. Insulin resistance is found in 50% to 90% of these women.[3-5] PCOS is thought to confer a risk of insulin resistance above and beyond that caused by obesity.[6,7] The risk of hypertension is increased 3-fold, that of type 2 diabetes mellitus 6-fold, and of coronary artery disease 7-fold.[8,9] In addition, inadequately treated PCOS carries a risk of endometrial cancer.

In this study, our goal was to examine in a clinical setting several of the endocrine and metabolic parameters detailed above. We characterized these women in terms of age, obesity, insulin resistance, pancreatic β-cell function, ovarian and adrenal androgen production, adrenal responses to corticotropin (ACTH) administration, and lipid profiles to identify factors possibly contributing to morbidity. Our primary goal was to determine whether insulin resistance was a predictor of comorbid factors. Upon finding a close correlation between insulin resistance and obesity, we explored the relative effects of insulin resistance versus body mass index (BMI) on the above factors.

SUBJECTS AND METHODS

We conducted an Institutional Review Board-approved retrospective chart review of patients presenting to Stanley G. Korenman's university-based reproductive endocrinology clinic with chief complaints of hirsutism, alopecia, acne, or weight gain. A broad definition of PCOS was used, so that we could study women in all stages of the disorder. Criteria defining eligibility were similar to those of the 1990 National Institute of Child Health and Human Development Consensus Conference,[2] 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 bioavailable testosterone or adrenal androgen, such as dehydroepiandrosterone (DHEA) or dehydroepiandrosterone sulfate (DHEA-S). Oligo-ovulation was considered to be present if the patient gave a history of a reduced frequency of menses or a history of difficulty becoming pregnant. We included hyperandrogenic women who reported regular menses since some patients with PCOS have regular cycles, but are oligo-ovulatory documented by luteal phase progesterone measurements.[10]

Patients were not included if they had a hyperandrogenic disorder other than PCOS, such as Cushing's syndrome, 21-hydroxylase deficiency, or hyperandrogenic insulin resistance acanthosis nigricans syndrome (HAIR AN). 21-hydroxylase deficiency presenting as adult-onset (nonclassical) adrenal hyperplasia was diagnosed using standard criteria.[11,12] We excluded 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 without treatment. Such medications included oral contraceptives, metformin, glucocorticoids, and dexamethasone. Patients were excluded if they had impaired fasting glucose, diabetes mellitus, hypopituitarism, prolactinoma, active thyroid disease, or anorexia nervosa. In light of the above entry and exclusion criteria, 69 cases of PCOS (of 143 charts reviewed) were deemed appropriate for inclusion in this study.

Anthropometric and laboratory data were always measured during

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Table 1. Anthropometric and Metabolic Comparison of IS and IR Patients With PCOS

	Age (yr)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Glucose (mg/dL)	Fasting Insulin (μIU/mL)	Glucose/Insulin Ratio	HOMA IR	HOMA β-Cell (%)
All (N = 69)	27.1	163.9	82.7	30.6	89.0	15.1	10.3	3.15	210.8
IS (n = 46)	27.3	162.6	72.3	27.5	87.4	7.8	13.1	1.69	126.1
IR (n = 23)	26.7	166.7	103.7	37.1	92.8	29.6	3.7	6.70	415.9
P value*	.74	.057	<.0001	<.0001	.021	<.0001	<.0001	<.0001	<.0001

*Insulin sensitive *v* insulin resistant.

Abbreviations: IS, insulin sensitive; IR, insulin resistant.

initial evaluation, before institution of any therapy. A clinic nurse obtained the weight, height, and systolic and diastolic blood pressure of each subject. Age at time of presentation is reported here, and BMI is calculated as kg/m^2. All 69 patients underwent an extensive metabolic profile that included a morning fasting glucose, insulin, total and bioavailable testosterone (BT), and an ACTH stimulation test. ACTH stimulation was performed the same morning as the other blood tests and consisted of measurement of DHEA, androstenedione (A4), 17-hydroxyprogesterone (17-OH-prog), 17-hydroxypregnenolone (17-OH-preg), and cortisol before and 1 hour after intravenous injection of 250 μg Cosyntropin ($ACTH_{1\text{-}24}$). A complete lipid panel (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglyceride [TG] level) was also available for 45 subjects; assayed by us or by the referring physician. Seven TG values were not analyzed because the patients were not fasting, and 1 LDL-C level was not available because this subject's TG level was above 400 mg/dL, preventing calculation of the LDL-C level. These 45 subjects did not differ from the whole group in age or any anthropometric or metabolic parameter. All of the above data were obtained by chart review of each patient's initial evaluation. Normal values were provided by the laboratory performing the blood tests (Quest Diagnostics, San Juan Capistrano, CA for hormonal measurements, all other tests at the UCLA Clinical Laboratory).

Insulin resistance is often assessed using a fasting morning glucose to insulin ratio (G:I, glucose in mg/dL, insulin in μIU/mL). A prior study determined that a ratio of 4.5 or less has a 95% sensitivity for detection of insulin resistance in obese women with PCOS.[13] Because the glucose to insulin ratio was validated only in obese women, we used the homeostasis model assessment (HOMA) to calculate an index of insulin resistance for each patient. HOMA equations predict the homeostatic concentrations that arise from varying degrees of insulin resistance and β-cell function with good correlation to euglycemic clamp studies[14] and have been used extensively to quantify insulin resistance in patients of any body mass. Comparison of the patient's fasting glucose and insulin with the model's predictions allows a quantitative assessment of both the patient's insulin resistance and their β-cell function. Using fasting glucose in mmol/L and insulin in μIU/mL, the index for insulin resistance, HOMA IR, is defined as (insulin $\times$ glucose)/22.5 and HOMA β-cell function = 20 $\times$ insulin/(glucose-3.5). An ideal, normal-weight person aged < 35 years has a HOMA IR = 1 and HOMA β-cell function = 100%.[15]

Data from NHANES III[16] was used to obtain a population of normal women for comparison to women with PCOS. Subjects from NHANES III who had glucose and insulin levels obtained after at least 8 hours fasting were selected to match the age and racial/ethnic distribution of the PCOS group. Thus, the groups were comparable in age (NHANES mean age, 27.3; range, 15 to 40; PCOS mean age, 27.1; range, 13 to 46). Both populations had equal proportions of Caucasian subjects (64%), Mexican-Americans (11%), African-Americans (9%), and other ethnic groups (16%). Those who were using insulin or who had a fasting glucose > 110 mg/dL (6.1 mmol/L) or a glycosylated hemoglobin > 6% were excluded from analysis to remove individuals with glucose intolerance or diabetes, yielding 1,257 subjects for analysis. The methods used for glucose, insulin, and lipid levels are detailed in the NHANES report.[16]

Statistical Analysis

Student's *t* test was used to compare means between groups. Parameters that had a skewed distribution (weight, BMI, insulin, glucose to insulin ratio, HOMA IR, HOMA β-cell function, and all testosterone and adrenal androgen values) were first log transformed before application of Student's *t* test or calculation of the coefficient of correlation. A P value < .05 was considered statistically significant. Multiple regression analysis was conducted with HOMA IR and BMI (both log transformed) as independent variables and lipid, blood pressure, and androgen indices (log transformed) as separate dependent variables. This gave the relative effects of HOMA IR and BMI on these parameters. An F test was used to compare regression coefficients between women with PCOS and women from NHANES. Analyses were conducted using Statview 5.01 and SAS software (SAS Institute, Cary, NC).

RESULTS

Insulin Resistance

By selection, no patient met criteria for impaired fasting glucose (110 to 125 mg/dL or 6 to 7 mmol/L) or diabetes mellitus (>125 mg/dL or 7 mmol/L). However, HOMA IR values indicated a wide range of insulin resistance from 0.53 to 13.3. The most insulin-resistant tertile of patients (n = 23) had HOMA IR values ranging from 3.5 to 13.3. This group, defined as the insulin-resistant group, was compared with the remainder of the patients, termed the insulin-sensitive group (n = 46). The HOMA IR values for the insulin sensitive group ranged from 0.53 to 3.3. Table 1 compares the insulin-resistant group and the insulin-sensitive groups. The largest differences were found in terms of parameters of insulin resistance, β-cell function, and BMI. β-cell function was very different between the groups, with a normal mean of 126% for the insulin-sensitive group and an elevated mean of 416% in the insulin-resistant group ($P < .0001$). For all PCOS patients, there was a significant correlation ($r = .78$, $P < .0001$) between HOMA IR and HOMA β cell (Fig 1A).

The insulin-resistant and sensitive groups did not differ in terms of age, height, or racial/ethnic distribution; however, the insulin-resistant group had a much higher BMI. There was a significant correlation between BMI and HOMA IR ($r = .55$, $P < .0001$, Fig 1B).

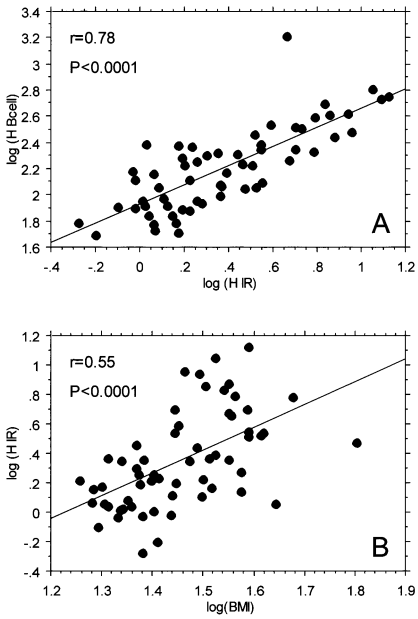

Fig 1. Informative correlations observed in patients with PCOS. (A) Correlation between HOMA IR and HOMA β-cell function. (B) Correlation between BMI and HOMA IR.

Bioavailable Testosterone and Adrenal Hormones

The insulin-resistant and sensitive groups had similar total testosterone levels (39 ng/dL *v* 47 ng/dL, $P = .43$), yet the insulin-resistant group had a higher percent BT (28% *v* 16%, $P < .0001$), resulting in higher mean BT levels than in the insulin-sensitive group (10.8 ng/dL *v* 7.2 ng/dL, $P = .0016$). Among all patients with PCOS, there was a correlation ($r = .39$, $P = .0017$) between BT and HOMA IR. A stronger correlation was observed between HOMA IR and percent BT ($r = .55$, $P < .0001$). Adrenal androgens and androgen precursors were assayed at baseline and after ACTH stimulation. Basal adrenal androgen levels did not differ by insulin sensitivity. Comparing the insulin-resistant and sensitive groups, the ACTH-stimulated DHEA level was higher in the insulin-resistant group (24.9 ng/mL *v* 16.4 ng/mL, $P = .011$); stimulated 17-OH-preg levels were similar between the insulin-sensitive and resistant groups (1017 ng/dL *v* 985 ng/dL, $P = .73$).

Cardiovascular Risk Factors

Lipid profiles were available for 45 patients (Table 2). The mean total cholesterol level was 192 mg/dL (4.9 mmol/L), mean LDL-C 116 mg/dL (3.0 mmol/L), mean HDL-C 50 mg/dL (1.3 mmol/L), and mean TGs 129 mg/dL (1.5 mmol/L). A consistent trend toward greater cardiovascular risk was revealed in comparing the insulin-resistant and sensitive groups; the total cholesterol was 201 mg/dL (5.1 mmol/L) versus 186 mg/dL (4.7 mmol/L) ($P = .16$), LDL-C 121 mg/dL (3.1 mmol/L) versus 114 mg/dL (2.9 mmol/L) ($P = 0.49$), HDL-C 43 mg/dL (1.1 mmol/L) versus 54 mg/dL (1.4 mmol/L) ($P = .0075$), TGs 196 mg/dL (2.2 mmol/L) versus 90 mg/dL (1.0 mmol/L) ($P = .0005$), total/HDL-C 4.8 versus 3.7 ($P = .0028$). Nineteen of 45 total cholesterol assays were $\geq$ 200 mg/dL (5.2 mmol/L), 5 of 44 LDL assays were $\geq$ 160 mg/dL (4.1 mmol/L), 20 of 45 HDL assays were $\leq$ 45 mg/dL (1.2 mmol/L), and 12 of 38 TG assays were $\geq$ 150 mg/dL (1.7 mmol/L).

Systolic blood pressure (SBP) was significantly higher in the insulin-resistant group (119.5 *v* 108.6 mm Hg, $P = .00086$) as was diastolic blood pressure (DBP, 77.3 *v* 71.1 mm Hg, $P = .012$). Eight patients had an elevated blood pressure, defined as SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg; 6 of these patients were insulin resistant. One insulin-resistant patient carried a prior diagnosis of hypertension. Of the patients who had follow-up blood pressure measurements, 1 insulin-sensitive patient remained hypertensive on no medications, while 3 insulin-resistant patients had normalization of blood pressure after starting metformin-based therapy.

The average BMI for all the PCOS patients was 30.6 kg/m^2, with 44 of the 69 patients (64%) overweight or obese with a BMI $>$ 25 kg/m^2.[17] BMI ranged from 19 to 64 kg/m^2 in the insulin-sensitive group and 28 to 59 kg/m^2 in the insulin-resistant group. The average BMI in the insulin-sensitive group was 27.5 kg/m^2, while in the insulin-resistant group, it was 37.1 kg/m^2. Of the 46 insulin-sensitive patients, 21 (46%) had a BMI 25 to 30 kg/m^2, and 13 (28%) had a BMI $>$ 30 kg/m^2. Among the 23 insulin-resistant patients, all were overweight and 20 (87%) had a BMI $>$ 30 kg/m^2.

Relative Effects of BMI Versus HOMA IR on Cardiovascular Risk Factors

The observed burden of elevated androgen levels, elevated TGs, depressed HDL-C, and higher blood pressure in the insulin-resistant group led us to assess the relative contribution of insulin resistance and BMI to these parameters, especially because BMI and HOMA IR were correlated (Fig 1B). We used age- and ethnically-matched normoglycemic women from NHANES III as a reference population. Table 3 gives the results of regressions of lipid parameters and blood pressure levels on HOMA IR and BMI jointly. For PCOS women, the

Table 2. Cardiovascular Risk Factor Comparison of IS and IR Patients With PCOS

	SBP (mm Hg)	DBP (mm Hg)	Total Cholesterol (mg/dL)	LDL Cholesterol (mg/dL)	HDL Cholesterol (mg/dL)	Triglycerides (mg/dL)	Total/HDL Ratio
All (N = 45)	112.2	73.1	191.5	116.3	50.0	128.9	4.1
IS (n = 28)	108.6	71.1	185.5	113.7	54.0	89.9	3.7
IR (n = 17)	119.5	77.3	201.4	121.0	43.4	195.9	4.8
P value*	.00086	.012	.16	.49	.0075	.0005	.0028

*Insulin sensitive *v* insulin resistant.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3. Relative Effects of BMI and HOMA IR on Blood Pressure and Lipid Risk Factors Analyzed by Multiple Regression

	PCOS (n = 69)				NHANES (n = 1,257)			
	BMI		HOMA IR		BMI		HOMA IR	
Parameter	RC (SRC)	*P* Value	RC (SRC)	*P* Value	RC (SRC)	*P* Value	RC (SRC)	*P* Value
Systolic blood pressure	0.029 (0.07)	.65	0.045 (0.30)	.0529	0.078 (0.17)	<.0001	0.027 (0.15)	.0002
Diastolic blood pressure	0.058 (0.12)	.44	0.033 (0.2)	.21	0.078 (0.11)	.0075	0.042 (0.15)	.0002
Total cholesterol	0.18 (0.25)	.16	0.02 (0.08)	.66	0.20 (0.22)	<.0001	0.01 (0.03)	.46
LDL-C	0.34 (0.29)	.11	0.021 (0.05)	.79	0.30 (0.21)	<.0001	0.028 (0.05)	.31
HDL-C	0.009 (0.009)	.96	−0.17 (−0.44)	.013	−0.22 (−0.18)	<.0001	−0.12 (−0.24)	<.0001
Triglycerides	0.19 (0.08)	.64	0.57 (0.57)	.0014	0.65 (0.27)	<.0001	0.20 (0.21)	<.0001
Total/HDL ratio	0.16 (0.13)	.44	0.20 (0.43)	.012	0.41 (0.28)	<.0001	0.13 (0.23)	<.0001

NOTE. The standardized regression coefficient allows direct comparison, within a given patient group, of the magnitude of the effects of the independent variables on the dependent variable. Significant coefficients are indicated in bold.

Abbreviations: RC, regression coefficient; SRC, standardized regression coefficient.

HOMA IR coefficients for HDL-C, TGs, and total/HDL-C ratio were significant. The coefficient for SBP was almost significant ($P = .0529$). In contrast, none of the BMI coefficients were significant for any of the dependent variables. This suggested that among PCOS women HOMA IR was more important than BMI in predicting cardiovascular risk factors, at least for the 4 with significant or nearly significant HOMA IR coefficients. Table 3 also gives regression results for the NHANES women. Because of its much larger sample size, almost all of the regression coefficients were significant. BMI was more important than HOMA IR in predicting most of the cardiovascular risk factors in NHANES. All significant and nearly significant HOMA IR coefficients in PCOS were larger than the corresponding coefficients in NHANES (Table 4). For example, the coefficients for TGs were 0.57 and 0.20, respectively. An F test for equality of these coefficients had a *P* value of .008, which showed that the PCOS coefficient was significantly greater than the NHANES coefficient. For the other cardiovascular risk factors, the differences were not statistically significant, but as noted in each case, the coefficients were larger for PCOS than NHANES. To illustrate this differential effect of HOMA IR, Fig 2 presents overlaid partial regression plots for the PCOS and NHANES risk factor regressions listed in Table 4. These plots depict the effect of incremental increases in HOMA IR on the various cardiovascular risk factors, at any given level of BMI. The greater effect of HOMA IR on TGs in PCOS is reflected in the steeper slope of the regression line for PCOS (Fig 2C), indicating that, at any level of BMI, a given increase in HOMA IR results in a larger increment in TG level in PCOS than NHANES.

Androgen levels were not available for women from NHANES. Among the women with PCOS, multiple regression showed insulin resistance effects on BT and %BT ($P = .053$ and .0006). BMI had no significant effects on BT or %BT ($P = .44$ and .34).

Table 4. F Tests for the Significance of the Differences in the HOMA IR Coefficients in the PCOS and NHANES Regressions for the Risk Factors With Significant PCOS HOMA IR Coefficients

Risk Factor	PCOS Coefficient	NHANES Coefficient	F Value	*P* Value
SBP	0.045	0.027	0.7	.40
HDL-C	−0.17	−0.12	0.6	.44
Triglycerides	0.57	0.20	7.1	.008
Total/HDL	0.20	0.13	1.0	.32

DISCUSSION

The Cardiovascular Dysmetabolic Syndrome

This study attempted to characterize hormonal and cardiovascular parameters in a group of patients with PCOS and to compare them with the cardiovascular characteristics of the putatively unbiased sample of similarly aged women from NHANES III. The analysis emphasized the relative importance of insulin resistance versus BMI in determining cardiovascular risk.

While not conclusive, our findings suggest that among PCOS women HOMA IR is a stronger predictor of cardiovascular risk factors than BMI, and that HOMA IR is a stronger predictor among PCOS women than among NHANES women. More specifically this applies to the risk factors SBP, HDL-C, TGs, and total/HDL. For the other risk factors, we have no results in this regard because their PCOS analyses had no significant coefficients.

These results are not inconsistent with previous reports, although previous comparisons produced conflicting results.[18-22] The use of women from NHANES provided a very large and solid normal control group, and 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. Nevertheless, we found provocative differences between the 2 groups.

We must ask whether the lipid values we found were "normal" for a group of women at a mean age of 27. For example, a mean total cholesterol of 192 mg/dL (4.9 mmol/L) may be elevated, and 42% of our patients had frankly elevated values over 200 mg/dL (5.2 mmol/L). The most important and significant abnormalities in the insulin-resistant group were in HDL-C and TGs, a characteristic of the cardiovascular dysmetabolic syndrome.[23] The elevated TGs in the syndrome are associated with small dense LDL, an independent predictor of cardiovascular disease,[24-26] raising the question of the extent to

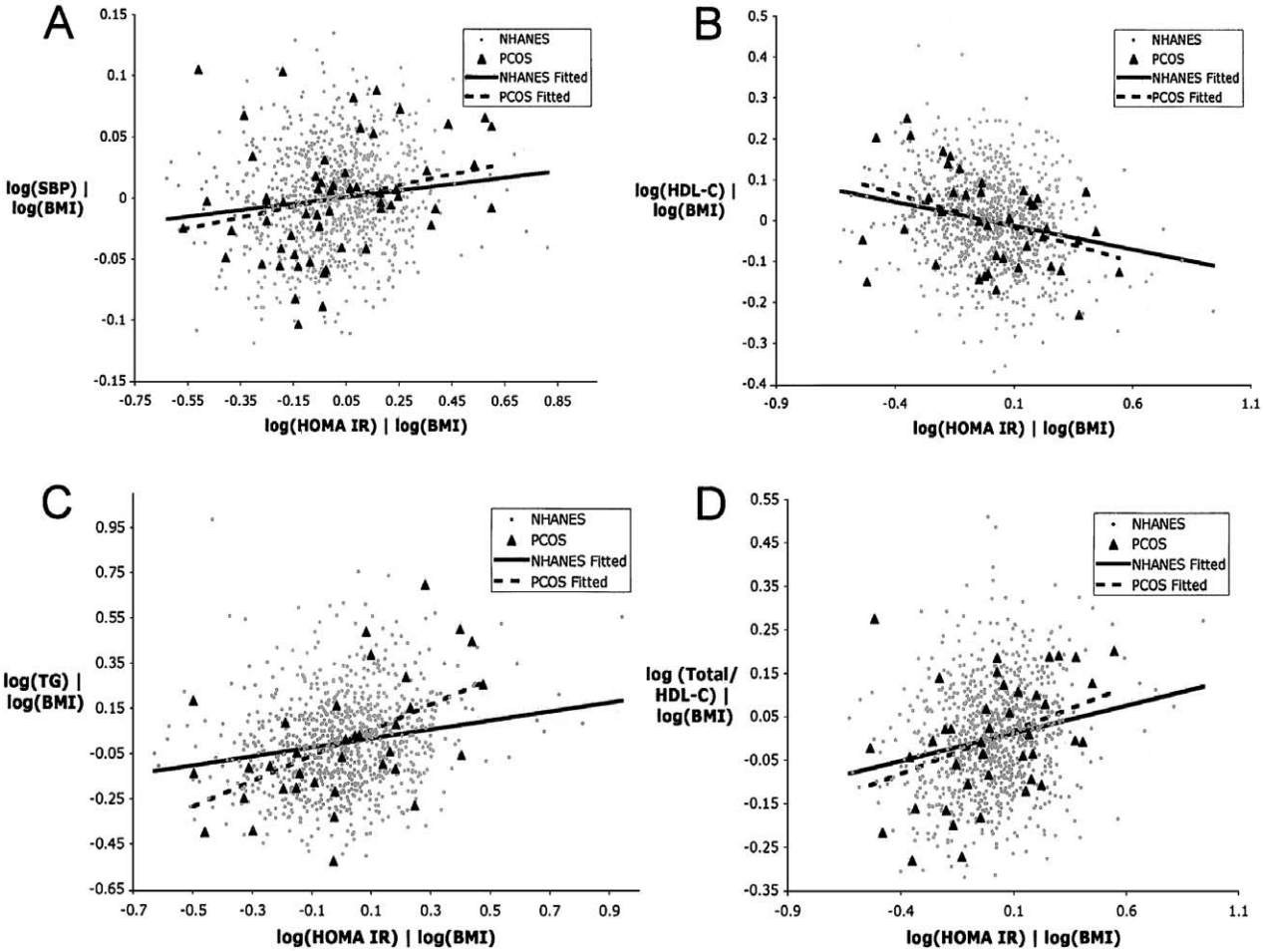

Fig 2. Partial regression plots of HOMA IR on the cardiovascular risk factors that had significant PCOS HOMA IR coefficients. Each plot is an overlay of the partial regression plot for PCOS and for NHANES. (A) SBP. (B) HDL-C. (C) TGs. (D) Total cholesterol/HDL-C ratio.

which these insulin resistance-related findings are responsible for the increased cardiovascular disease seen in PCOS.

Compared with insulin-sensitive patients, the insulin-resistant patients had higher SBPs and DBPs and a much higher mean BMI. Blood pressure levels were not influenced by body mass after adjustment for HOMA IR in women with PCOS. Several patients already had hypertension. Most of these were insulin resistant, and several had normalization of blood pressure after starting treatment with metformin (data not shown). We do not know whether this effect was mediated through insulin sensitization or weight loss.

Insulin Resistance

We used the HOMA IR to categorize our patients, because this tool has been shown to be a reliable reflection of insulin resistance with a good correlation (r = .6 to .88) with the euglycemic hyperinsulinemic glucose clamp procedure.[15,27] A recent study showed HOMA IR to have a better correlation with clamp results than even indices using oral glucose tolerance tests.[14] We found that a HOMA IR cutoff of 3.5 identified the most insulin-resistant tertile of patients, which was also the group with the largest burden of deranged blood pressure, lipid, and androgen levels. We believe that the wide range of observed HOMA IR values is a reflection of the broad inclusion criteria that incorporated women at all stages of the disorder. Alternatively, women diagnosed with PCOS may represent a pathologically heterogeneous group, with insulin resistance playing a critical role in some, but not all, cases.

Because the patients had normal fasting glucose levels (range, 69 to 105 mg/dL or 3.8 to 5.8 mmol/L), they had adequate β-cell function. As seen in Fig 1A, as insulin resistance worsens, there is a compensatory β-cell response that overcomes the insulin resistance, resulting in normal glucose levels. The most insulin-resistant patients with PCOS in this study had β cells producing up to 6 times as much insulin as the sensitive group. These patients are likely to be at increased risk of β-cell exhaustion and development of type 2 diabetes mellitus.[28] A recent 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.[29] The fact that our insulin-resistant group had slightly higher glucose

levels (Table 1) than the insulin-sensitive group suggests that such β-cell failure may be forthcoming.

Some studies suggest that insulin resistance may cause hyperandrogenemia,[30,31] while others suggest the reverse.[32,33] The current study found a modest correlation ($r = .39$) between HOMA IR and BT and a stronger correlation ($r = .55$) between HOMA IR and %BT. As total testosterone levels were similar in the insulin-sensitive and resistant groups, the higher BT in the insulin-resistant group is a result of the higher %BT. Both obesity and hyperinsulinemia may contribute to decreased levels of sex hormone-binding globulin (SHBG), resulting in a higher %BT. It has been suggested that hyperinsulinemia may mediate the decrease in SHBG seen with increasing adiposity.[34] Multiple regression of BMI and HOMA IR showed that HOMA IR, but not BMI, correlated with %BT ($P = .0006$ for HOMA IR, $P = .34$ for BMI). Thus, in PCOS, insulin resistance or the resultant hyperinsulinemia contributes significantly to depressed SHBG. Insulin suppresses hepatic synthesis of SHBG.[18]

In comparing the insulin-resistant and sensitive groups, the resistant group had a significantly higher post-ACTH DHEA response. Whether insulin resistance or hyperinsulinemia influences adrenal androgen secretion has not been established. 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.[35]

Clinical Implications

These data verify that PCOS warrants aggressive therapy to prevent serious cardiovascular complications and diabetes mellitus. All patients require assessment for insulin resistance and dyslipidemia. Obese patients with PCOS must be encouraged to diet and exercise, especially since weight loss may lead to improvements in insulin resistance, hypercholesterolemia, and hyperandrogenism. Failure to lose weight is partly attributable to the metabolic abnormalities in PCOS and partly due to accompanying depression. Patients should have at least a fasting glucose and insulin for detection of insulin resistance; a recent study suggests that oral glucose tolerance testing is more sensitive in detection of impaired glucose tolerance in adolescents with PCOS.[36] Insulin sensitization therapy with metformin has been found to lower testosterone levels, increase SHBG, improve menstrual frequency, decrease weight, and result in pregnancy.[37,38] Metformin is also associated with increased HDL-C, decreased LDL-C, and decreased TGs.[39] Tertiles of HOMA IR among Pima Indians identified low, medium, and high risk for progression to diabetes mellitus.[14] A HOMA IR > 3.5 identified the most insulin-resistant tertile in our study. The middle tertile of our patients had HOMA IR values from 1.6 to 3.5. Studies are needed to demonstrate whether metformin use in these PCOS patients with milder insulin resistance will inhibit progression to severe insulin resistance.

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