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Does Polycystic Ovarian Syndrome Increase Insulin Resistance Above and Beyond Obesity?

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Abstract

Objective: Although obesity and insulin resistance are common in women with polycystic ovarian syndrome (PCOS), PCOS is generally believed to independently raise the risk of insulin resistance. However, only a few studies have used direct measures of insulin resistance, and they have included few subjects. The objective of this study was to compare the relationship between body mass index (BMI) and insulin resistance in a relatively large sample size of women, with and without PCOS, using a specific measure of insulin action.

Methods: We compared 94 women with PCOS based on the 1990 NIH criteria with 72 controls with eumenorrhea less than 40 years old. Degree of insulin resistance was quantified using the insulin suppression test. Fasting glucose and lipid concentrations and blood pressure were also measured.

Results: There was a significant and comparable relationship between BMI and insulin resistance in women with and without PCOS (r=0.55, p<0.001 in PCOS, r=0.53, p<0.001 in Control). In a linear model adjusted for age and BMI, PCOS was not significantly associated with insulin resistance. PCOS was significantly associated with systolic blood pressure (p=0.03) but not triglyceride, high-density lipoprotein cholesterol and fasting glucose concentration.

Conclusion: Challenging previous studies, we find that PCOS is not independently associated with insulin resistance beyond obesity. PCOS, however, may independently increase systolic blood pressure.

Keywords: Insulin resistance; PCOS; Obesity; Blood pressure

Abbreviations:

BMI: Body Mass Index; LDL-C: Low-density Lipoprotein Cholesterol; HDL-C: High-density Lipoprotein Cholesterol Concentration; PCOS: Polycystic Ovarian Syndrome; SSPG: Steady-state Plasma Glucose

Introduction

Between 40-60% of women with polycystic ovarian syndrome (PCOS) in the United States are obese [1,2]. Although obesity increases the risk for insulin resistance in both populations with [3] and without [4] PCOS, PCOS is often considered to independently increase the risk of insulin resistance [3,5-8]. However, only a few studies have evaluated the effect of PCOS on insulin resistance using direct methods to measure insulin resistance [3,5-7]. In addition, these studies have been limited by small sample size (16-43 women with PCOS). Finally, available studies have compared mean degrees of insulin resistance between women with and without PCOS matched for body mass index (BMI) without considering the relationship between obesity and insulin resistance.

The purpose of this study was to evaluate the relationship between obesity and insulin resistance using a direct measure of insulin resistance in 94 women with PCOS compared with 72 controls. In addition, we evaluated the independent association between PCOS and several metabolic variables which have been related to insulin resistance (including blood pressure, fasting plasma glucose and lipid indices) and described to be abnormal in women with PCOS [9-11]. To the best of our knowledge, this represents the largest study of women with PCOS using a specific measure of insulin resistance and conducting these types of analyses.

Materials and Methods

Subjects

Women with PCOS (n=94) and controls (n=72) were selected through our registry of past volunteers who have had a measure of insulin resistance. Other criteria for inclusion were as follows: age 18-39 years, fasting glucose <126 mg/dL, no personal history of diabetes, and not taking medications affecting carbohydrate metabolism (e.g., metformin).

All women were previously recruited through newspaper advertisements for studies approved by the Stanford Institutional Review Board. PCOS was defined according to the 1990 National Institute of Child Health and Human Development consensus criteria [12]. Therefore, women with PCOS had oligomenorrhea or amenorrhea (eight or fewer menses per year, or ≥45 mean days between bleeding episodes) and either clinical or biochemical evidence of hyperandrogenism.

The control group was made up of 72 women who were premenopausal and eumenorrheic.

Clinical measures

All women were evaluated in the Stanford Clinical Research Center after fasting for 12 hours. The following procedures were performed on the same day: measurement of height, weight, and blood pressure; blood draw for lipid panel; and insulin suppression test for measurement of insulin resistance. Before measurement of blood pressure, study volunteers were seated quietly in a chair for 5 minutes with feet on the floor and one arm supported at heart level. Using a Dinamap automatic blood pressure recorder (GE Healthcare, Tampa, FL) with appropriately-sized cuff, 3 blood pressure readings were taken at 1-minute intervals, and the mean of these readings was used for data analysis.

Insulin resistance was measured using the insulin suppression test [13] which is highly correlated with the euglycemic clamp [14]. Briefly, a constant infusion of octreotide (0.27 μg/m²/minute), insulin (32 mU/m²/minute), and glucose (267 mg/m²/minute) were administered via an intravenous line for 180 minutes to achieve steady-state glucose and insulin levels. Plasma glucose concentrations were measured at baseline and every 10 minutes from 150 to 180 minutes and averaged to obtain the steady-state plasma glucose (SSPG) concentration. As steady-state plasma insulin concentrations are comparable among individuals and glucose infusion rate is identical, the SSPG concentration provides a direct measure of insulin resistance; the higher the SSPG concentration, the more insulin resistant the individual.

Glucose was measured by the oxidase method. Lipid measurements were performed by the core laboratory at Stanford University Medical Center and included low-density lipoprotein cholesterol (LDL-C), triglyceride and high-density lipoprotein cholesterol concentration (HDL-C).

Statistical Analysis

All statistical analysis was performed using SPSS (version 16 for Windows; SPSS, Chicago, IL). Descriptive data are presented as mean ± SD unless otherwise stated. Comparisons between PCOS and controls were performed using independent t tests. A linear model was used to assess the effect of PCOS on the relationship between BMI and SSPG (insulin resistance). The effect of PCOS on several metabolic measures (blood pressure, fasting plasma glucose, triglyceride and HDL-C) was also evaluated unadjusted and adjusted for age and insulin resistance. We also evaluated the interaction between PCOS status and insulin resistance by multiplication.

Results

In this population of women less than 40 years old, women with PCOS were somewhat younger (Table 1). Although mean BMI was in the obese category in both groups, women with PCOS were heavier. Women with PCOS had higher systolic blood pressure but other measures, including SSPG, were not significantly different between groups.

	PCOS	Control	Pa
N	94	72	
Age	29 ± 6	33 ± 4	<0.001
BMI (kg/m2)	34.3 ± 9.2	31.5 ± 6.8	0.03
Systolic Blood Pressure	120 ± 16	113 ± 12	0.003
Diastolic Blood Pressure	70 ± 11	68 ± 8	0.24
Pulse	74 ± 12	73 ± 11	0.64
Fasting Plasma Glucose (mg/dL)	94 ± 9	92 ± 8	0.12
Triglyceride (mg/dL)	97 [62, 155]	101 [65, 152]	0.74
HDL-C (mg/dL)	46 ± 12	47 ± 13	0.80
LDL-C (mg/dL)	112 ± 28	108 ± 31	0.38
SSPG (mg/dL)	200 ± 82	178 ± 74	0.08

Table 1: Characteristics of the PCOS and control women

Data are mean ± SD or median [interquartile range]. aIndependent t-test comparing PCOS and control women.

Figure 1 illustrates the relationship between BMI and insulin resistance in women with and without PCOS. BMI was positively and comparably associated with SSPG in both groups (r=0.55, p<0.001 in PCOS, r=0.53, p<0.001 in Control). The relationship between BMI and insulin resistance was similar between PCOS and control women regardless of age stratification or obesity status (Table 2). In addition,

PCOS was not an independent predictor of SSPG in a linear model adjusted for age and BMI (p=0.79).

	PCOS	Control	Pa
All	0.55 (0.39-0.68) (n=94)	0.53 (0.34-0.68) (n=72)	0.86
Age ≤ 30	0.57 (0.36-0.72)	0.49 (0.03-0.78)	0.70

	(n=57)	(n=18)	
Age >30	0.53 (0.25-0.73) (n=37)	0.55 (0.22-0.65) (n=54)	0.68
BMI <30	0.34 (0.01-0.61) (n=35)	0.41 (0.07-0.66) (n=32)	0.75
BMI ≥ 30	0.38 (0.13-0.58) (n=59)	0.35 (0.04-0.59) (n=40)	0.87

Table 2: Univariate correlations between BMI and Insulin Resistance in PCOS and control women

Data are Pearson's r-value (95% confidence interval). aIndependent t-test comparing PCOS and control women.

We also evaluated the association between PCOS and several metabolic variables unadjusted and adjusted for age and insulin resistance (Table 3). PCOS was significantly associated with systolic blood pressure even after adjustment for age and insulin resistance. There were no other significant associations. In addition, there were no interactions between PCOS and insulin resistance in predicting any of the metabolic variables ($p \geq 0.15$).

	Beta Coefficient	SE	P
Systolic Blood Pressure			
Unadjusted	6.50	2.25	0.004
Adjusted	4.99	2.27	0.03
Diastolic Blood Pressure			
Unadjusted	1.64	1.55	0.29
Adjusted	1.77	1.56	0.26
Fasting Plasma Glucose			
Unadjusted	2.06	1.33	0.12
Adjusted	2.53	1.32	0.06
Triglyceride			
Unadjusted	-0.04	0.10	0.71
Adjusted	-0.08	0.09	0.35
HDL-C			
Unadjusted	-0.32	1.92	0.87
Adjusted	1.31	1.91	0.50

Table 3: Association between PCOS and metabolic abnormalities unadjusted and adjusted for age and insulin resistance

Discussion

In our two study groups, there was a six-fold range in the degree of insulin resistance (SSPG 50-300 mg/dL, Figure 1), and both women with and without PCOS were found at the lower and higher end of insulin resistance. BMI explained roughly 25% of the variance in insulin resistance as measured by the insulin suppression test. This degree of association between BMI and insulin resistance has been demonstrated in other populations where insulin resistance has been directly quantified [4]. PCOS itself, however, was not independently associated with insulin resistance. In addition, with the exception of systolic blood pressure, PCOS was not independently associated with several metabolic variables related to insulin resistance.
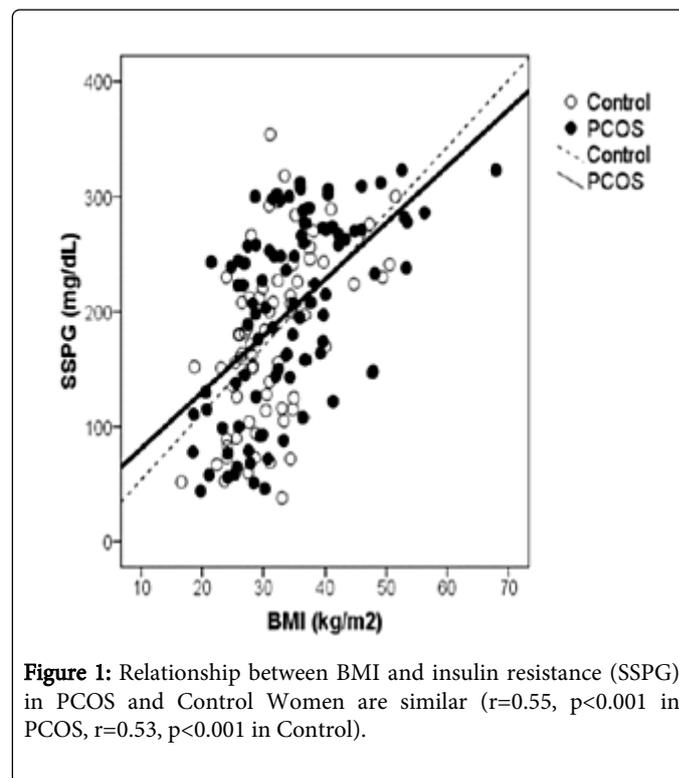

Figure 1: Relationship between BMI and insulin resistance (SSPG) in PCOS and Control Women are similar (r=0.55, p<0.001 in PCOS, r=0.53, p<0.001 in Control).

Although obesity is a known risk factor for insulin resistance in both populations with [3] and without [4] PCOS, several studies have suggested that women with PCOS are at an increased risk for insulin resistance independent of obesity [3,5-8]. However, among the studies that have used direct measures of insulin resistance, the sample sizes have been small (16-43 women with PCOS). In addition, they did not compare the relationship between BMI and insulin resistance in women with and without PCOS [3,5-7]. For example, Dunaif et al. evaluated 29 women with PCOS compared with 19 controls [5]. Using the hyperinsulinemic euglycemic clamp, they showed that obese and lean women with PCOS had lower insulin sensitivity compared with control women. Although women with and without PCOS were matched for body composition, obese women with PCOS were heavier than the control women (mean BMI 35.6 kg/m2 versus 30 kg/m2). This difference in BMI was not statistically significant likely due to their small sample size; however, the magnitude of difference in BMI was double that found between groups in our study (5.6 vs. 2.8 kg/m2). Therefore, the difference in adiposity may have contributed to some of the difference in insulin resistance found between women with and without PCOS.

The fact that PCOS is not independently associated with insulin resistance should not diminish the clinical impact of insulin resistance on PCOS. Although insulin can augment androgen production in both women with and without PCOS, women with PCOS may have a hyperresponsiveness for insulin-mediated androgen synthesis [15]. For example, Asagami et al. demonstrated that insulin-resistant

women had higher testosterone concentration compared with insulin-sensitive women regardless of PCOS status. However, in that study, the difference in testosterone concentration between insulin-resistant and insulin-sensitive women was much greater in women with PCOS than control groups, suggesting a magnified androgen response to insulin in women with PCOS. Therefore, although insulin resistance may not be a unique feature of PCOS, the consequence of insulin resistance and associated hyperinsulinemia on androgen production may be greater in PCOS women than controls.

Although the effects of insulin resistance on androgen production may be magnified in PCOS, PCOS was not uniquely associated with several metabolic variables related to insulin resistance, with the exception of systolic blood pressure. Past studies have produced mixed results on the association between PCOS and blood pressure with both significant [16,17] and null [18-21] associations. While this may be related to the heterogeneity in the populations evaluated, the majority of these past studies did not control for insulin resistance. We identified only one study that had quantified insulin resistance using a specific measure of insulin resistance [17] and also blood pressure in women with and without PCOS. Similar to our study, they found a significantly elevated systolic but not diastolic blood pressure even when adjusted for insulin resistance as measured using the euglycemic clamp. Systolic blood pressure, therefore, may be independently associated with PCOS.

A potential limitation of this study is that we lacked hormonal evaluation of andrgens in the two groups, as patients were diagnosed with PCOS clinically. Although not the primary focus, this information would have allowed us to investigate the relationship between insulin resistance and androgen concentration and the potential impact of androgen concentration on metabolic abnormalities (e.g. blood pressure). We also did not have waist measurements in our two groups. However, in past studies, BMI and waist circumference have had a similar relationship with insulin resistance as measured by the insulin suppression test [4]. Therefore, it is unlikely that the availability of waist measurements would have produced different results than seen with BMI. Finally, we chose to use the NIH criteria to diagnose PCOS as opposed to the Rotterdam [22] or Androgen Excess Society [23] criteria. These latter criteria capture a broader phenotype of PCOS and may also identify women with less metabolic abnormalities than the NIH criteria [24]; therefore, our choice of PCOS definition is unlikely to have underestimated the relationship between obesity and insulin resistance.

In conclusion, although insulin resistance is often considered a hallmark or universal [9] feature of PCOS, we did not find an independent association between PCOS and insulin resistance. In both populations with and without PCOS, the degree of insulin resistance was heterogeneous and associated with degree of obesity. Insulin resistance status, therefore, should not be assumed based on PCOS status alone.

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Author Contributions

MT collected data and wrote the manuscript; SHK contributed to design and conduct of the study, data collection and analysis, data interpretation, and manuscript writing.

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