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# Relationship among obesity, insulin resistance, and hyperinsulinemia in the polycystic ovary syndrome

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## Abstract

**Purpose** To evaluate the relationship between obesity and insulin resistance among women with polycystic ovary syndrome (PCOS) using a gold standard test.

**Methods** A retrospective database analysis of 75 women with PCOS and 118 normal controls who underwent a modification of the insulin suppression test. The relationships between body mass index (BMI) and steady-state plasma glucose (SSPG) levels were investigated.

**Results** Mean SSPG score for PCOS subjects was statistically similar than that of the controls at all BMI groupings. Only when PCOS subjects reached a BMI of ≥30 kg/m$^2$ that the PCOS subjects had higher mean SSPG score than the control subjects, although not significantly so ($p = 0.07$). The distribution of PCOS and control subjects in each SSPG quartile grouping was investigated. When comparing all PCOS and control subjects, PCOS subjects were more likely to be in the higher quartiles of SSPG score ($p = 0.0001$). However, when comparing the PCOS and control subjects, at each BMI grouping (<25, 25–29.9, and ≥30 kg/m$^2$), there was no difference in the likelihood that a larger percent of subjects fell into a different quartile ($p = 0.12$, 0.69, 0.32, respectively).

**Conclusions** PCOS subjects have increased magnitudes of insulin resistance when compared to ovulatory controls, when controlling for age, BMI, fasting glucose, and insulin levels. However, the magnitude of this insulin resistance in lean subjects is mild. Quantity of excess body fat, particularly subjects with a BMI of at least 30 kg/m$^2$ is the primary predictor of insulin resistance of sufficient magnitude to put PCOS subjects at increased risk for metabolic abnormalities.

**Keywords** PCOS · Insulin resistance · Insulin suppression test · Obesity · BMI

## Introduction

Although there is general acceptance that patients with polycystic ovary syndrome (PCOS) tend to be overweight, insulin resistant, and hyperinsulinemic, the relationship among these variables remains controversial, as does the link between the metabolic abnormalities and the hyperandrogenic state. Part of this uncertainty can be attributed to use of surrogate estimates of insulin resistance in many studies, but results obtained with the hyperinsulinemic, euglycemic clamp, often referred to as the "gold standard" measure of insulin action, have not been consistent. Thus, Dunaif et al. [1] in a relatively small study, in which insulin resistance was quantified with the hyperinsulinemic, euglycemic clamp, concluded that "PCO women have a significant insulin resistance that is independent of obesity." The view that insulin resistance is characteristic of PCOS was supported by the findings of Guler and colleagues [2], also using the "clamp" technique, showing that non-obese individuals with PCOS ($n = 12$) were significantly more insulin resistant than age- and obesity-matched control group ($n = 10$). However, results of a study by Ovesen et al. [3], which was very similar to that of Guler and colleagues [2], came to a diametrically opposite finding, namely, that non-obese persons with PCOS were not insulin resistant when compared to age- and weight-matched controls. Two other "clamp" studies [4, 5], both relatively large, also came to the conclusion that insulin resistance in individuals with

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PCOS was confined to the subset of those who were also overweight/obese.

In addition to discordant findings concerning the presence of insulin resistance in non-obese individuals with PCOS, differences also exist in the relationship between insulin resistance and hyperinsulinemia in non-obese persons with PCOS. Compensatory hyperinsulinemia not only permits insulin-resistant individuals to avoid gross decompensation of glucose tolerance [6] but it also appears to play a major role in the pathogenesis of the hyperandrogenism in PCOS [7, 8]. The presence of hyperinsulinemia in insulin-resistant subjects with PCOS is straightforward. However, hyperinsulinemia was also described in two of the three "clamp" studies in which non-obese individuals with PCOS were found to be normally insulin sensitive [4, 5]. In the absence of insulin resistance, it seems necessary to postulate that non-obese individuals with PCOS are either secreting insulin disproportionately to their degree of insulin resistance and/or have a defect in insulin clearance. The current analysis was undertaken to address these unresolved questions concerning the relationship between adiposity, insulin resistance, and plasma insulin concentration. It differs from published information in that the experimental population is approximately twice as large as any previous study in which a specific method was used to quantify insulin resistance. It should also be noted that this study was performed using insulin-mediated glucose uptake as opposed to euglycemic clamp studies, commonly used in other published studies, as noted above.

## Material and methods

A retrospective database query was performed to identify patients with PCOS and normal ovulatory control subjects between the ages of 18 and 40 years, who had a quantitative measurement made of insulin-mediated glucose uptake (IMGU) and BMI.

IMGU was quantified by a modification of the insulin suppression test (IST) as originally described and validated [9–11]. Briefly, subjects were infused for 180 min with octreotide (0.27 μg/m$^2$/min), insulin (25 mU/m$^2$/min), and glucose (240 mg/m$^2$/min). Blood was drawn at 10-min intervals from 150 to 180 min of the infusion to measure plasma glucose and insulin concentrations, and the mean of these four values used as the steady-state plasma insulin (SSPI) and glucose (SSPPG) concentrations for each individual. As SSPI concentrations are similar in all subjects during these tests (~60μU/ml), the steady-state plasma glucose (SSPG) concentration provides a load; the higher the SSPG concentration, the more insulin resistant the individual. As part of the validation procedure, it was shown that the results of measurements of IMGU with the IST were highly correlated ($r$ values >0.95) with those obtained with euglycemic hyperinsulinemic clamp studies.

Patients with PCOS were oligovulatory (menstrual cycles less frequent than every 35 days) or anovulatory, with clinical (Ferryman–Gallway score ≥8) or biochemical evidence (serum total testosterone or free testosterone levels greater than female assay maximum) of hyperandrogenism.

Control participants were ovulatory with regular menstrual cycles occurring every 21 to 35 days and premenstrual molimina. The control participants also lacked clinical and biochemical evidence of hyperandrogenism (total testosterone <60 ng/ml, free testosterone <2 ng/ml, dehydroepiandrosterone sulfate (DHEAS) <271 μg/dl).

In addition, all subjects lacked clinical or biochemical evidence of thyroid abnormalities (0.39< thyroid-stimulating hormone >4.0 μIU/ml); hyperprolactinemia (a.m. fasting prolactin <26 ng/ml); hypothalamic pituitary dysfunction and ovarian failure (1.4< follicle-stimulating hormone >20mIU/ml and estradiol >20 pg/ml); ovarian and adrenal androgen-secreting tumors (total testosterone <200 ng/ml and DHEAS <800 μg/dl); and non-classical congenital adrenal hyperplasia (a.m. fasting 17-hydroxy-progesterone <3 ng/ml).

Finally, subjects were excluded from analysis is they had diabetes mellitus as determined by a 75-g oral glucose tolerance test with normal stimulated and fasting blood glucose levels, participated in another research study in the last 30 days, and if they had used hormones or other medications, which may affect reproductive or metabolic function within 60 days of the study.

All statistical analyses were done using the statistical package for social sciences 11.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were evaluated for normal distribution using the Kolmogorov–Smirnov test. Results are reported as mean value ± standard deviation (SD). Continuous variables were compared by stepwise logistic regression to control for confounding effects. The confounding effects controlled for were interactions between age in years, BMI, SSPG result, fasting serum glucose, and fasting serum insulin levels (Tables 1 and 2). In addition to

**Table 1** A comparison of demographics in the PCOS and control subjects

| | PCOS ($N = 75$) | Control ($N = 118$) | $P$ value |
|---|---|---|---|
| Age (years) | 30 ± 6 | 35 ± 7 | 0.0001 |
| BMI (kg/m$^2$) | 34.5 ± 9.2 | 25.9 ± 5.9 | 0.0001 |
| SSPG (mg/dl) | 188 ± 87 | 136 ± 74 | 0.0001 |
| Fasting glucose (mg/dl) | 94 ± 8 | 86 ± 10 | 0.0001 |
| Fasting insulin (μU/ml) | 21 ± 14 | 11 ± 6 | 0.0001 |

Logistic regression performed, controlling for confounding effects between all variables listed in this table

*PCOS* polycystic ovary syndrome, *BMI* body mass index, *SSPG* steady-state plasma glucose

**Table 2** A comparison of demographics in the PCOS and control subjects matched for BMI

| | PCOS ($N = 46$) | Control ($N = 46$) | $P$ value | Confidence interval |
|---|---|---|---|---|
| Age (years) | 30 ± 6 | 32 ± 7 | 0.018 | 0.84–0.98 |
| BMI (kg/m$^2$) | 30.9 ± 7.1 | 29.8 ± 6.7 | 0.36 | 0.96–1.13 |
| SSPG (mg/dl) | 169 ± 84 | 160 ± 81 | 0.035 | 1.01–1.17 |
| Fasting glucose (mg/dl) | 95 ± 9 | 88 ± 10 | 0.006 | 1.03–1.16 |
| Fasting insulin (μU/ml) | 17 ± 12 | 13 ± 6 | 0.17 | 0.98–1.15 |

Logistic regression performed, controlling for confounding effects between all variables listed in this table

*PCOS* polycystic ovary syndrome, *BMI* body mass index, *SSPG* steady-state plasma glucose

the analysis of continuous variables, the control patients were divided into quartiles for their SSPG concentrations. The quartiles of the SSPG results for the control subjects were used to determine the normal range of SSPG values into which the PCOS patients were subdivided. PCOS and control subjects were organized into percent of subjects with a specific BMI grouping who fell into each of these quartiles. The number of subjects in a quartile among the PCOS and control populations was compared by $\chi^2$ tests. Statistical significance was accepted as a two-sided $p \le 0.05$. Approval from the Stanford University Institutional Review Board had been obtained for collection and analysis of these data.

## Results

Seventy-five women with PCOS and 118 normal controls had their data analyzed in the study. Demographics for both groups are presented in Table 1. It should be noted that the two groups differed for all variables analyzed. To determine whether SSPG would remain greater when controlling for age and BMI in PCOS compared to controls, stepwise logistic regression analysis was performed for this table. SSPG score remained greater among the PCOS subjects when compared to controls ($p = 0.0001$).

We subsequently matched PCOS and controls for BMI ±2 kg/m$^2$ and repeated the analysis to confirm that SSPG would remain greater when controlling for age, fasting glucose, insulin levels, and BMI. We were able to match 46 controls and PCOS for BMI. Results are presented in Table 2. The SSPG score remained greater among the PCOS subjects when compared to controls matched for BMI.

Among controls, 59 (50%) have a BMI <25 kg/m$^2$, 29 (25%) have a BMI 25–29.99 kg/m$^2$, and 30 (25%) have a BMI ≥30 kg/m$^2$. Eight (11%) of the PCOS subjects have a BMI of <25 kg/m$^2$, 17 (23%) have a BMI 25–29.99 kg/m$^2$, and 50 (67%) have a BMI ≥30 kg/m$^2$. A comparison of PCOS and control subjects with BMI of <25 kg/m$^2$, 25–29.99 kg/m$^2$, and ≥30 kg/m$^2$ is presented in Table 3. It should be noted that the mean SSPG score for PCOS subjects was statistically similar than that of the controls at all BMI groupings. It was only when PCOS subjects reached a BMI of ≥30 kg/m$^2$ that the PCOS subjects had a higher mean SSPG score than the control subjects, although not significantly so ($p = 0.07$).

Control subjects were divided into three groups based on quartiles of SSPG score. The percent of PCOS and control subjects whose SSPG score was within each quartile is presented in Table 4. As expected, when comparing all PCOS and control subjects, PCOS were more likely to be in the higher quartiles of SSPG score ($p = 0.0001$). However, when comparing the PCOS and control subjects, at each BMI grouping (<25, 25–29.9 and ≥30 kg/m$^2$), there was no statistical difference in the likelihood that a larger percent of subjects fell into a different quartile ($p = 0.12$, 0.69,0.32, respectively).

## Discussion

These data confirm that PCOS patients have on average a greater defect in IMGU as measured by the SSPG when compared to controls (Table 4), even when controlling for BMI, age, fasting glucose, and insulin levels (Table 1). This has been previously demonstrated in studies using both surrogate markers of IMGU and euglycemic hyperinsulinemic clamp studies [1, 3]. However, at all BMIs patients with PCOS seem as likely as control subjects to fall in each of the SSPG quartiles (Table 3). It is important to note that all PCOS patients with a BMI <25 kg/m$^2$ fell in the lowest 50% of control measures of SSPG. This suggests that few PCOS subjects with BMI <25 kg/m$^2$ are at increased risk for metabolic abnormalities caused by the magnitude of their insulin resistance. It should be acknowledged that this conclusion is based on a relatively modest population of PCOS subjects ($N = 8$) and may change slightly if the population studied was enlarged. Clearly, even the controls with BMI <25 kg/m$^2$ ($N = 59$) had <35% of subjects in the highest 50% for SSPG score, suggesting that most lean subjects are not at risk for metabolic derangements induced by hyperinsulinemia.

Interestingly, at a BMI of 25–29.99 kg/m$^2$, PCOS subjects start to demonstrate increased fasting glucose levels,

**Table 3** Comparison of metabolic characteristics as a function of BMI

| Variable | BMI category (kg/m$^2$) | | | | | |
|---|---|---|---|---|---|---|
| | BMI <25 | | 25≤BMI<30 | | BMI ≥30 | |
| | PCOS ($N = 8$) | Control ($N = 59$) | PCOS ($N = 17$) | Control ($N = 29$) | PCOS ($N = 50$) | Control ($N = 30$) |
| SSPG (mg/dl) | 84 ± 20 | 103 ± 46 | 134 ± 73 | 149 ± 73 | 223 ± 75 | 188 ± 87 |
| Fasting glucose (mg/dl) | 87 ± 6 | 82 ± 9 | 94 ± 8* | 87 ± 8 | 94 ± 8 | 92 ± 10 |
| Fasting insulin (μU/ml) | 8 ± 2 | 9 ± 4 | 13 ± 8 | 10 ± 5 | 26 ± 15** | 15 ± 7 |

*$p < 0.005$

**$p = 0.001$

Analysis controlled for age and BMI

**Table 4** Distribution of BMI as a function of SSPG quartile

| BMI (kg/m$^2$) | Quartile 1, 25–69 mg/dl | | Quartile 2, 70–122 mg/dl | | Quartile 3, 123–185 mg/dl | | Quartile 4, 186–346 mg/dl | | *P* value |
|---|---|---|---|---|---|---|---|---|---|
| | PCOS | Control | PCOS | Control | PCOS | Control | PCOS | Control | |
| <25 | $N = 2$ (25%) | $N = 19$ (32%) | $N = 6$ (75%) | $N = 20$ (34%) | — | $N = 17$ (29%) | — | $N = 3$ (5%) | 0.12 |
| 25–29.9 | $N = 4$ (24%) | $N = 7$ (24%) | $N = 5$ (29%) | $N = 5$ (17%) | $N = 4$ (24%) | $N = 6$ (21%) | $N = 4$ (24%) | $N = 11$ (38%) | 0.69 |
| ≥30 | $N = 1$ (2%) | $N = 2$ (7%) | $N = 5$ (10%) | $N = 6$ (20%) | $N = 10$ (20%) | $N = 7$ (23%) | $N = 34$ (68%) | $N = 15$ (50%) | 0.32 |
| Total | $N = 7$ (9%) | $N = 28$ (24%) | $N = 16$ (21%) | $N = 31$ (26%) | $N = 14$ (19%) | $N = 30$ (25%) | $N = 38$ (51%) | $N = 29$ (25%) | 0.0001 |

but not insulin levels, when compared to controls (Table 2). Even at a BMI <25 kg/m$^2$, this relationship occurred when comparing the PCOS and controls, although sub-significant ($p = 0.06$). This finding suggests a possible defect with hyper-insulin secretion. While at a BMI ≥30 kg/m$^2$, PCOS subjects when compared to control subjects exhibit hyperinsulinemia, which is out of proportion to the magnitude of their BMI (Table 3). These findings suggest that it is only at a BMI ≥30 kg/m$^2$ that PCOS subjects have a hyperisulinemia of sufficient magnitude when compared to controls to have consequences for long-term health, which is of a magnitude that overcomes the effect of obesity.

The dichotomy in IMGU noted among controls with a BMI of at least 30 kg/m$^2$, where ~40% of subjects demonstrate SSPG scores in the lower half of IMGU does not occur in PCOS subjects. Only 12% of obese PCOS subjects have a SSPG score in the lower 50% of normal controls. Therefore, while a normal ovulatory women has a 40% chance of demonstrating a defect in IMGU, if their BMI is at least 30 kg/m$^2$, it can be assumed that a PCOS subject with a BMI of 30 kg/m$^2$ or greater has a defect in IMGU. On the other hand, this is not necessarily true for leaner PCOS subjects (Table 4), where ~50% of PCOS subjects with a BMI of 25–29.99 kg/m$^2$ fell in the upper 50% of SSPG scores of the normal controls.

Although it appears from Table 3 that the rates of insulin resistance among the PCOS subjects is not greater than the controls, this is due to the facts that we have chosen arbitrary cut-offs for SSPG values and the small number of PCOS subjects with BMI <25 kg/m$^2$. It does not take into consideration different BMI distributions in the three groupings used (<25, 25–29.9, and ≥30 kg/m$^2$).

Although it can be considered that the number of patients with a BMI under 25 ($N = 8$) is a weakness for our conclusion, PCOS subjects with normal BMI show a low risk of developing metabolic disorders. It should also be noted that the group with a BMI of 25–29.99 kg/m$^2$ also did not have an increased risk of the metabolic syndrome. This raises the total number of patients in the group on with we drew the conclusion to 33 from 8, and now constitutes 33% of the total PCOS study population, bolstering our conclusion. Nevertheless, a large study should be performed to confirm these results.

In conclusion, PCOS subjects have increased magnitudes of insulin resistance when compared to ovulatory controls, when controlling for age, BMI, fasting glucose, and insulin levels (Table 1). This finding was also confirmed when matching subjects for BMI (Table 2). However, the magnitude of this insulin resistance in lean subjects is mild (Tables 3 and 4). The quantity of excess body fat, particularly subjects with a BMI of at least 30 kg/m$^2$, is the primary predictor of insulin resistance of sufficient magnitude to put PCOS subjects at increased risk for metabolic abnormalities (Tables 3 and 4), when not accounting for hyperandrogenic-induced changes.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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