Markers of Insulin Resistance Predict Metabolic Syndrome in Women with Polycystic Ovary Syndrome

Martha W. Noel1*, Chia-Ning Kao1, Kanade Shinkai2, Lauri A. Pasch3, Marcelle I. Cedars1, and Heather G. Huddleston1

1Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, USA
2Department of Dermatology, University of California, USA
3Department of Psychiatry, University of California, USA

Abstract

Objective: To study the relationship between markers of insulin resistance and metabolic syndrome components in patients with polycystic ovary syndrome (PCOS).

Design: Cross-sectional study.

Setting: Tertiary academic institution.

Patients: 265 non-diabetic women aged 15-52 years old with PCOS by Rotterdam criteria examined between 2006 and 2013.

Intervention(s): Receiver operator characteristic (ROC) curves were calculated for fasting insulin (FI) and homeostatic model assessment of insulin resistance (HOMA-IR) to determine their value in predicting metabolic syndrome in this patient population.

Main outcome measure(s): Blood pressure, waist circumference, fasting lipids, fasting glucose, 75-gram oral glucose tolerance test.

Results: Women with PCOS with FI > 13 mIU/L and/or HOMA-IR >3.4 have a 6-fold higher incidence of metabolic syndrome when compared to PCOS patients with values below these thresholds. In a multivariate logistic regression controlling for age and body mass index (BMI), elevated FI and HOMA-IR were associated with significantly increased risk of metabolic syndrome (OR 2.92 and 3.30, respectively) as well as increased risk of individual component of the syndrome. PCOS patients with elevated markers of insulin resistance also demonstrated an impaired response to an oral glucose tolerance test. No differences were seen in testosterone, sex hormone binding globulin, or rates of oligo/anovulation or polycystic appearing ovaries.

Conclusion: In the PCOS population, simple, clinically obtained measures of insulin resistance can be used to identify women at higher risk for metabolic syndrome and metabolic derangement. This can be used to stratify patients for more intensive counseling, follow-up and to encourage lifestyle modifications.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrinopathy affecting 6-10% of reproductive age women [1]. PCOS is characterized by the classic triad of ovulatory dysfunction, hyperandrogenemia and polycystic ovarian morphology; using the criteria established by the Rotterdam consensus in 2003, two of the above three findings must be met to establish the diagnosis [2]. Women with PCOS are also at high risk for metabolic abnormalities, in particular insulin resistance and compensatory hyperinsulinemia, independent of obesity [3,4]. Insulin resistance is hypothesized to be intrinsic to the pathophysiology of PCOS, perhaps by stimulating theca cell hyperplasia and increasing production of ovarian androgens, as well as by decreasing levels of sex-hormone binding globulin. On a molecular level, studies have demonstrated intrinsic post-receptor defects signaling causing disruption in insulin signaling in women with PCOS [5]. Serine phosphorylation of the insulin receptor leads to decreased activation of the PI3-K pathway, reducing GLUT-4 translocation to the cell membrane and leading to increased resistance to insulin’s metabolic actions. Simultaneously, constitutive activation of the mitogenic MAPK pathway has been found in the skeletal muscle of women with PCOS, which further
increases insulin receptor serine phosphorylation. Depending on the PCOS sub-population evaluated and the way in which insulin resistance is measured, rates of insulin resistance are estimated to be between 40-70% [6,7]. Consequently, women with PCOS have an increased prevalence of impaired glucose tolerance and type 2 diabetes, when compared to the general population [8-11]. A recent meta-analysis showed a 2.5-fold increase in impaired glucose tolerance and a 4-fold increase in type 2 diabetes in women with PCOS compared to BMI-matched controls [12]. Due to the association between metabolic disorders, diabetes and cardiovascular disease, there has been recent emphasis on screening and identification of these disorders in women with PCOS [13].

Insulin resistance is also thought to contribute to the development of metabolic syndrome. The National Cholesterol Education Program Adult Treatment Program III (NCEP ATP III) criteria defines metabolic syndrome as the presence of three or more of the following components: waist circumference >88 cm, triglycerides ≥150 mg/dL, HDL cholesterol <50 mg/dL, blood pressure ≥130/85 mmHg, and fasting glucose ≥110 mg/dL [14]. Women with PCOS are also at higher risk for metabolic syndrome. Rates of metabolic syndrome in women with PCOS ranges from approximately 8-53%, which is 2- to 10-fold higher than in the general population depending on the control group used for comparison [15-19].

Data from a non-PCOS population have shown that the presence of insulin resistance can predict the development of metabolic disorders such as hypertension, type 2 diabetes, and cardiovascular disease [20]. To date, there have been few studies evaluating the predictive value of insulin resistance on the presence of metabolic syndrome PCOS patients. Furthermore, the cut-off for these markers that might indicate higher risk for metabolic dysregulation has not yet been established. Ersan et al. examined the association of HOMA-IR, adiponectin and leptin with metabolic syndrome in 91 women with PCOS [21]. They found that HOMA-IR was significantly associated with metabolic syndrome, and that a HOMA-IR value of > 2.51 had 87% sensitivity and 74% specificity for predicting metabolic syndrome. This study was somewhat limited by its relatively small sample size, as only 15 women were diagnosed with metabolic syndrome. A more recent, larger study comparing PCOS patients to controls found that HOMA-IR was associated with an increased risk of metabolic syndrome, with an odds ratio of 4.1 [22]. This study was conducted in an Iraqi population with a high rate of metabolic syndrome in their control group (32.7%) and therefore may not be able to be extrapolated to a more heterogeneous US population.

Our objective was to determine the value of markers of insulin resistance in predicting metabolic syndrome in women with PCOS, and to determine cut-offs that help identify patients with metabolic syndrome. We also sought to identify the degree of metabolic dysregulation in PCOS patients with elevated markers of insulin resistance when compared to those without.

**MATERIALS AND METHODS**

**Subjects**

This study received Institutional Board Review approval from the Committee on Human Research at the University of California, San Francisco. This study was designed as a cross-sectional cohort study of patients prospectively and consecutively recruited in a multidisciplinary PCOS clinic at our tertiary referral academic center between 2006 and 2013. The study population was referred for evaluation of symptoms suggestive of PCOS. Patients diagnosed with PCOS by the 2003 Rotterdam criteria (anovulation or oligo-ovulation with < 8 cycles per year; clinical hyperandrogenism with acne vulgaris, hirsutism or androgenic alopecia or biochemical hyperandrogenism with total or free testosterone, dehydroepiandrosterone-sulfate [DHEA-S] or androstenedione greater than the reference range of the reporting laboratory; polycystic appearing ovaries with ≥12 follicles in either ovary and/or ovarian volume ≥10 cm³) met with a study coordinator who consented them to participate in the cohort study. On average, 80% of women seen in the PCOS clinic signed informed consent to participate in the study. Patients who consented to participate had a systematically collected questionnaire, ultrasound, fasting blood and other clinical data entered into a database. In this analysis, patients were excluded if they had overt diabetes diagnosed by fasting blood sugar ≥126 mg/dL. Routine screening for other disease states that may be mistaken for PCOS was performed, including hypothalamic hypogonadism by follicle stimulating hormone and estradiol, congenital adrenal hyperplasia by 17-hydroxyprogesterone, hyperprolactinemia by prolactin, androgen-producing adrenal tumors by total and free testosterone and DHEA-S, and thyroid dysfunction by thyroid stimulating hormone. Patients were excluded from analysis if they were confirmed to have any of these disorders.

**Clinical, anthropomorphic and biochemical evaluation**

At our multi-disciplinary PCOS clinic, patients present for a one-time visit at which, following completion of an extensive questionnaire, they undergo a detailed history and physical examination including a transvaginal ultrasound to determine ovarian morphology and antral follicle count. Endovaginal ultrasounds are performed by one of two examiners (HGH or MIC) using a Shimadzu SDU-450XL machine with a variable 4- to 8-mHz vaginal transducer. Cutaneous measures of hyperandrogenism, including hirsutism as measured by modified Ferriman-Gallway score, acne vulgaris and androgenic alopecia, are determined by a single dermatologist (KS). Anthropomorphic measurements taken are height, weight, waist circumference and blood pressure. Serum measurements are obtained at commercial laboratories based on individual insurance plans and include fasting lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), fasting glucose and insulin, glucose and insulin following a two-hour 75-gram oral glucose tolerance test, free and total testosterone, dehydroepiandrosterone-sulfate, androstenedione, and sex hormone binding globulin (SHBG). Three primary laboratories (Quest, LabCorp and UCSF) are utilized to obtain approximately 75% of the insulin assays; these laboratories utilize liquid chromatography/tandem mass spectrometry (LC/MS-MS) or electrochemiluminescence immunoassay (ECLIA) to measure insulin values. Markers of insulin resistance evaluated for the purposes of this study
were fasting insulin and HOMA-IR. HOMA-IR was calculated by the formula ((fasting insulin (mIU/L) x fasting glucose (mg/dL))/405).

**Main outcome measures**

All patients who met inclusion criteria were assessed for metabolic syndrome. Metabolic syndrome was defined using 2001 NCEP ATP III criteria by the presence of three or more of the following components: waist circumference >88 cm, triglycerides ≥150 mg/dL, HDL cholesterol <50 mg/dL, blood pressure ≥130/85 mmHg, and fasting glucose ≥110 mg/dL. ROC curves were generated and used to calculate the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of fasting insulin and HOMA-IR for metabolic syndrome in this PCOS cohort. Using an ANCOVA model controlling for age and BMI, anthropomorphic measurements, lipids, response to oral glucose tolerance test, androgens, presence of biochemical/clinical hyperandrogenism, presence of oligo/anovulation and presence of polycystic appearing ovaries were compared in PCOS patients using fasting insulin or HOMA-IR thresholds established by ROC curve analysis. Logistic regression was used to evaluate the effect of fasting insulin and HOMA-IR on metabolic syndrome and its components in women with PCOS while controlling for age and BMI.

**Statistical analysis**

Statistical analyses were performed using SAS version 9.4 (Cary, NC). The predictive performances of fasting insulin and HOMA-IR for metabolic syndrome were assessed by constructing ROC curves. AUC and 95% confidence intervals were reported. The optimal thresholds for sensitivity and specificity were determined using the distance from the diagonal and the Youden index. Patients were divided into groups based on whether their fasting insulin or HOMA-IR values were above or below these thresholds. Each marker of insulin resistance was analyzed separately. Student’s t-test, chi-square or Fisher’s exact test were used to compare baseline characteristic data across groups. ANCOVA or logistic regressions were used to compare metabolic variables between groups after controlling for age and BMI. Multivariate logistic regression was performed to calculate odds ratios for the impact of fasting insulin and HOMA-IR on metabolic syndrome and its individual components, after controlling for age and BMI.

**RESULTS AND DISCUSSION**

**Results**

Between 2006 and 2013, 265 women were diagnosed with PCOS by the 2003 Rotterdam criteria. Of these, 31 women (11.7%) were found to have metabolic syndrome based on ATP III criteria.

The use of fasting insulin and HOMA-IR as predictors of metabolic syndrome was evaluated by constructing an ROC curve. The AUC for fasting insulin and HOMA-IR identifying metabolic syndrome was 0.766 (CI 0.667-0.866) and 0.770 (CI 0.671-0.869), respectively (Figure 1a). Optimal thresholds for fasting insulin and HOMA-IR that maximized sensitivity and specificity were identified at fasting insulin cut-off level of 13 mIU/L (sensitivity 77.4%, specificity 70.1%) and HOMA-IR of 3.4 (sensitivity 70.9%, specificity 78.2%) (Figure 1b). These thresholds were used to divide the patient population into groups based on their fasting insulin and HOMA-IR values. Of the 265 women with PCOS, 171 had a fasting insulin of ≤13 mIU/L and 94 had a fasting insulin of >13 mIU/L; 192 had a HOMA-IR score of ≤3.4 and 73 had a HOMA-IR score of >3.4.

Table 1 summarizes the baseline characteristics of the

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**Figure 1**

(A) – Receiver operating characteristic (ROC) curve analysis to determine the performance of fasting insulin and HOMA-IR as predictors for metabolic syndrome in women with PCOS. AUC with 95% CI are shown. Threshold values identified by the inflection point with maximal sensitivity and specificity. (B) – Sensitivity, specificity, positive predictive value and negative predictive value of fasting insulin >13 mIU/L and HOMA-IR >3.4 for metabolic syndrome in women with PCOS.
entire population and of each of the study groups as determined by fasting insulin and HOMA-IR thresholds. The mean age in the study cohort (n=265) was 28.5 years (range 14-52) and the mean BMI was 29.7 kg/m² (range 16-60). Patients with normal fasting insulin or HOMA-IR were significantly younger than patients with elevated fasting insulin or HOMA-IR (mean age 27.8 vs. 29.9 years, p<0.01, and 27.8 vs. 30.5 years, p<0.01, respectively). There were also significant differences in BMI between patients in the normal and elevated fasting insulin or HOMA-IR groups (mean BMI 26.6 vs. 35.4 kg/m², p<0.01, and 27.2 vs. 36.5 kg/m², p<0.01, respectively). The majority of patients with normal fasting insulin or HOMA-IR were normal weight/overweight (75.9% and 72.3%, respectively), while the majority of patients with abnormal fasting insulin or HOMA-IR were obese/morbidly obese (70.2% and 74%, respectively). There were no differences seen in ethnicity or in current or past tobacco use between the study groups.

We then compared rates of metabolic syndrome using the thresholds established by ROC curve analysis. The incidence of metabolic syndrome was 4.09% in patients with fasting insulin ≤13 mIU/L and 25.5% in patients with elevated fasting insulin >13 mIU/L. Similar rates of metabolic syndrome were seen in patients with HOMA-IR ≤3.4 compared to those with HOMA-IR >3.4 (4.69% vs. 30.1%, respectively).

Table (2) shows the comparison of all metabolic parameters between study groups. All comparisons were made after controlling for age and BMI with the exception of waist circumference, which was controlled for age alone. Compared to patients with fasting insulin ≤13 mIU/L, patients with elevated fasting insulin demonstrated a dysregulated response to an oral glucose challenge test as evidenced by significantly higher levels of two-hour insulin (p<0.0001) and two-hour glucose (p=0.0006). They also showed significantly decreased HDL levels (p=0.03), significantly elevated triglycerides (p=0.007), waist circumference (p<0.0001), and systolic blood pressure (p=0.02). No differences were seen in androgens or in sex hormone binding globulin, however, there was a small but significant increase in the number of women who met PCOS criteria for the diagnosis of biochemical/clinical hyperandrogenism (p=0.04). When other defining characteristics of PCOS were evaluated, no differences were found in rates of oligo-/anovulation or polycystic appearing ovaries. When compared to patients with HOMA-IR ≤3.4, patients with elevated HOMA-IR showed a similar trend to those with elevated fasting insulin, with the exception of HDL showing no significant difference, and diastolic blood pressure showing significant difference (p=0.03).

Finally, we examined the association between individual components of metabolic syndrome and elevated fasting insulin or HOMA-IR using multivariate logistic regression controlling for age and BMI (except waist circumference, corrected for age only). As expected, women with fasting insulin >13 mIU/L or HOMA-IR >3.4 showed a significantly increased risk of metabolic syndrome (OR 2.92, 95% CI 1.17-7.28, p=0.02, and OR 3.30, 95% CI 1.39-7.88, p=0.007, respectively). We also wanted to investigate the association between the individual abnormalities of metabolic syndrome with insulin resistance markers. As shown in Figure (2), significant associations between elevated fasting insulin or HOMA-IR and all individual components of metabolic syndrome were seen, with the exception of blood pressure (BP >130/85).

Discussion

We studied the predictive value of markers of insulin resistance, specifically fasting insulin and HOMA-IR, on identification of metabolic syndrome in women with PCOS diagnosed by the 2003 Rotterdam criteria. Our primary findings establish thresholds for fasting insulin and HOMA-IR that predict the presence of metabolic syndrome with >70% specificity and sensitivity. PCOS patients with elevated markers of insulin resistance are more likely to have elevated fasting insulin and HOMA-IR, which are strongly associated with metabolic syndrome.

### Table 1: Comparison of clinical characteristics of the study groups.

<table>
<thead>
<tr>
<th></th>
<th>All (n=265)</th>
<th>Fasting ≤13mIU/L (n=171)</th>
<th>Insulin &gt;13mIU/L (n=94)</th>
<th>HOMA-IR ≤3.4 (n=192)</th>
<th>HOMA-IR &gt;3.4 (n=73)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>28.5 (5.99)</td>
<td>27.8 (5.35)</td>
<td>29.9 (6.84)</td>
<td>27.8 (5.41)</td>
<td>30.5 (7.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.7 (7.94)</td>
<td>26.6 (5.73)</td>
<td>35.4 (8.22)</td>
<td>27.2 (5.95)</td>
<td>36.5 (8.55)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Normal (≤25)</td>
<td>31.3 (83)</td>
<td>43.9 (75)</td>
<td>8.5 (8)</td>
<td>40.6 (78)</td>
<td>6.8 (5)</td>
<td></td>
</tr>
<tr>
<td>Overweight (25-30)</td>
<td>27.9 (74)</td>
<td>31.6 (54)</td>
<td>21.3 (20)</td>
<td>31.3 (60)</td>
<td>19.2 (14)</td>
<td></td>
</tr>
<tr>
<td>Obese (&gt;30)</td>
<td>40.4 (107)</td>
<td>24.0 (41)</td>
<td>70.2 (66)</td>
<td>27.6 (53)</td>
<td>74.0 (54)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity, % (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>African-American</td>
<td>5.7 (15)</td>
<td>3.5 (6)</td>
<td>9.6 (9)</td>
<td>4.2 (8)</td>
<td>9.6 (7)</td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>18.1 (48)</td>
<td>17.0 (29)</td>
<td>20.2 (19)</td>
<td>18.2 (35)</td>
<td>17.8 (13)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>50.9 (135)</td>
<td>56.7 (97)</td>
<td>40.4 (38)</td>
<td>54.7 (105)</td>
<td>41.1 (30)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>12.8 (34)</td>
<td>11.1 (19)</td>
<td>16.0 (15)</td>
<td>11.5 (22)</td>
<td>16.4 (12)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12.5 (33)</td>
<td>11.7 (20)</td>
<td>13.8 (13)</td>
<td>11.5 (22)</td>
<td>15.1 (11)</td>
<td></td>
</tr>
<tr>
<td>Tobacco Use, % (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.66</td>
</tr>
<tr>
<td>Never</td>
<td>69.4 (184)</td>
<td>68.4 (117)</td>
<td>71.3 (67)</td>
<td>67.2 (129)</td>
<td>75.3 (55)</td>
<td></td>
</tr>
<tr>
<td>Current/Former</td>
<td>10.2 (27)</td>
<td>9.4 (16)</td>
<td>12.7 (11)</td>
<td>10.4 (20)</td>
<td>9.6 (7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>20.4 (54)</td>
<td>22.2 (36)</td>
<td>17.0 (16)</td>
<td>22.4 (43)</td>
<td>15.1 (11)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as mean (SE) or % (n). 
Superscript letters represent significant difference of p<0.01 (a: fasting insulin comparisons; b: HOMA-IR comparisons). 
P-values were obtained by chi-square or Fisher’s exact test.

**Abbreviations:** BMI: Body Mass Index; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance
Figure 2 Multivariate logistic regression model showing association between elevated fasting insulin or HOMA-IR and individual components of metabolic syndrome, controlling for age and BMI (except waist circumference, controlled for age only). 95% confidence intervals are depicted by whisker bars. Asterisk indicates significance at the p<0.05 level.

Table 2: Comparison of metabolic parameters between study groups.

<table>
<thead>
<tr>
<th>Metabolic Parameter</th>
<th>Fasting Insulin ≤13 mIU/L</th>
<th>Fasting Insulin &gt;13 mIU/L</th>
<th>p-value</th>
<th>HOMA-IR ≤3.4</th>
<th>HOMA-IR &gt;3.4</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>34.7 (0.8)</td>
<td>91.2 (1.1)</td>
<td>&lt;0.0001</td>
<td>84.4 (0.7)</td>
<td>93.9 (1.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Two-hour insulin</td>
<td>45.8 (9.3)</td>
<td>1.42 (14.5)</td>
<td>&lt;0.0001</td>
<td>52.5 (8.3)</td>
<td>158.8 (16.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Two-hour glucose</td>
<td>95.1 (2.6)</td>
<td>1.17 (3.8)</td>
<td>0.0006</td>
<td>96.0 (92.4)</td>
<td>113.9 (4.3)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>183.2 (2.8)</td>
<td>194.9 (4.1)</td>
<td>0.23</td>
<td>183.2 (2.6)</td>
<td>191.2 (4.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>104.8 (2.3)</td>
<td>105.8 (3.5)</td>
<td>0.38</td>
<td>104.6 (2.1)</td>
<td>110.1 (3.9)</td>
<td>0.22</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>59.7 (1.2)</td>
<td>54.9 (1.8)</td>
<td>0.03</td>
<td>59.0 (1.1)</td>
<td>55.6 (2.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>90.1 (7.4)</td>
<td>127.3 (11)</td>
<td>0.007</td>
<td>93.6 (7.0)</td>
<td>128.3 (12.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>80.8 (1.3)</td>
<td>100.6 (1.7)</td>
<td>&lt;0.0001</td>
<td>82.3 (1.3)</td>
<td>102.4 (2.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>107.6 (0.9)</td>
<td>111.5 (1.3)</td>
<td>0.02</td>
<td>108.0 (0.8)</td>
<td>111.6 (1.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>71.6 (0.6)</td>
<td>73.0 (0.9)</td>
<td>0.21</td>
<td>71.4 (0.6)</td>
<td>74.0 (1.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total testosterone</td>
<td>56.0 (2.6)</td>
<td>55.0 (3.8)</td>
<td>0.84</td>
<td>55.7 (2.4)</td>
<td>55.4 (4.2)</td>
<td>0.94</td>
</tr>
<tr>
<td>Free testosterone</td>
<td>6.4 (0.9)</td>
<td>6.2 (1.4)</td>
<td>0.88</td>
<td>6.4 (0.9)</td>
<td>6.3 (1.6)</td>
<td>0.99</td>
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<tr>
<td>SHBG (nmol/L)</td>
<td>50.0 (2.9)</td>
<td>52.5 (4.4)</td>
<td>0.63</td>
<td>50.6 (2.7)</td>
<td>51.5 (4.9)</td>
<td>0.87</td>
</tr>
<tr>
<td>Anovulation (%)</td>
<td>87.8 (144)</td>
<td>90.0 (81)</td>
<td>0.99</td>
<td>89.1 (164)</td>
<td>87.1 (61)</td>
<td>0.27</td>
</tr>
<tr>
<td>Biochemical/clinical HA (%)</td>
<td>86.6 (146)</td>
<td>93.6 (88)</td>
<td>0.0451</td>
<td>87.0 (167)</td>
<td>94.5 (59)</td>
<td>0.04</td>
</tr>
<tr>
<td>PCAO (%)</td>
<td>89.0 (146)</td>
<td>91.4 (7.5)</td>
<td>0.73</td>
<td>89.0 (161)</td>
<td>92.3 (60)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Data presented as mean (SE) or % (n). P-values were obtained from ANCOVA or logistic regression after correction for age and BMI. Superscript letter represents variables corrected for age only. NS represents p > 0.05. Counts may not total 100 due to few patients with missing data.

Abbreviations: HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; BP: Blood Pressure; SHBG: Sex Hormone Binding Globulin; HA: Hyperandrogenism; PCAO: Polycystic Appearing Ovaries

It is known that women with PCOS are at higher risk than the general population for metabolic syndrome. In our study of 265 PCOS patients, we found a prevalence of NCEP ATP III-diagnosed metabolic syndrome of 11.7%. This rate is at the lower end of what has been reported in studies of other PCOS cohorts, which can range from 8-53%. There are several possible reasons for this difference. Firstly, it may be due to the younger age and relatively low BMI of our cohort. In the previously cited 2005 study by Apridonidze et al. of 161 women with PCOS, the reported prevalence of metabolic syndrome was 45% in women age 20-29 years. However, approximately 60% of women in their study were obese or morbidly obese, which is a known risk factor for metabolic syndrome, as compared to 40% in our current study. The 2008 study of Australian women with PCOS reported rates of metabolic syndrome of 30-40%, depending on whether WHO, ATP III or IDF criteria were used, however their cohort was older with an average age of 34.3 years [19]. Secondly, our lower rate of metabolic syndrome may be due to the fact that we excluded patients with type 2 diabetes from our study. Though type 2 diabetes is also a risk factor for metabolic syndrome, we chose to exclude these patients given the potential for low fasting insulin and HOMA-IR in diabetic patients with pancreatic beta cell dysfunction [23]. PCOS patients with type 2 diabetes were included in both the Apridonidze study and in the 2005 study by Dokras et al. that reported a rate of metabolic syndrome of 20.2% in a PCOS cohort. Finally, we used the 2003 Rotterdam criteria to define our PCOS cohort, rather than the NIH criteria. One of the largest studies of metabolic syndrome in women with PCOS showed that rates are higher in patients identified by the NIH criteria [24]. In that study of approximately 1200 women, the rate of ATP III-defined metabolic syndrome was 17.1% when...
the NIH criteria were used as compared to 11.9% in patients diagnosed by Rotterdam criteria. In support of this hypothesis, in our study we found that of the three Rotterdam criteria, only the presence of clinical/biochemical hyperandrogenism was increased amongst patients with fasting insulin and HOMA-IR above our thresholds.

The thresholds we established for predicting metabolic syndrome in PCOS women were fasting insulin >13 mIU/L and HOMA-IR >3.4. Though simple to obtain, fasting insulin and HOMA-IR values have not traditionally been easy to interpret, particularly in PCOS patients, due to lack of established cut-offs for insulin resistance. The use of fasting insulin alone, in particular, is controversial and uncertainty exists regarding its utility as well as appropriate thresholds. Interestingly, we did not detect a difference between the two measures in their predictive ability, suggesting that in this case, fasting insulin may be as useful as HOMA-IR in identifying women with PCOS at risk for metabolic syndrome.

Insulin resistance is thought to be intrinsic to the pathophysiology of metabolic syndrome, and therefore is likely to be a good indicator of patient risk for this disorder. We found that patients with fasting insulin or HOMA-IR above our established thresholds had a 2.9- and 3.3-fold increased risk of having metabolic syndrome, respectively. Furthermore, we showed the risk of having each individual abnormality of the metabolic syndrome was increased, with the exception of blood pressure. Though our PCOS patients with fasting insulin and HOMA-IR above our cut-off values were slightly older and significantly more obese than PCOS patients with “normal” fasting insulin and HOMA-IR, we found these increased risks were independent of both age and BMI. We were able to identify only one other study in the literature that sought to determine the predictive value of either fasting insulin or HOMA-IR for metabolic syndrome in PCOS [21]. Their findings suggest that a HOMA-IR of ≥2.51 predicted metabolic syndrome with a sensitivity of 86%, specificity of 73%, and AUC of 0.833. The difference between the cut-offs established by their study and ours could be explained by the fact that theirs was a primarily Turkish population, and both HOMA-IR and the prevalence of metabolic syndrome have been shown to vary with ethnicity [25]. Our study cohort is both larger and multi-ethnic and therefore more broadly applicable to the general population.

In addition to higher risk of metabolic syndrome and its individual components, patients with fasting insulin and HOMA-IR above the thresholds we established also demonstrated poorer performance on the 75-gram oral glucose tolerance test. This was indicated by significantly higher levels of post-OGTT insulin and AUC of 0.833. The difference between the cut-offs established by their study and ours could be explained by the fact that theirs was a primarily Turkish population, and both HOMA-IR and the prevalence of metabolic syndrome have been shown to vary with ethnicity [25]. Our study cohort is both larger and multi-ethnic and therefore more broadly applicable to the general population.

CONCLUSION

In conclusion, we have shown that fasting insulin and HOMA-IR can be used as predictive markers for the presence of metabolic syndrome in women with PCOS. We have identified fasting insulin and HOMA-IR thresholds above which the risk for metabolic syndrome is increased, and have shown that patients with levels above these thresholds are also at increased risk of each of the individual components of metabolic syndrome (except blood pressure) as well as for impaired glucose tolerance,
REFERENCES