Insulin Resistance and β-cell Function Calculated by Homeostasis Model Assessment in Lean, Overweight, and Obese Women with Polycystic Ovary Syndrome

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OBJECTIVE: To evaluate the homeostasis model assessment (HOMA) measurement of insulin resistance (IR) and pancreatic β-cell function (%β) and compare those values between groups of healthy-weight, overweight, and obese women with polycystic ovary syndrome (PCOS).

STUDY DESIGN: Retrospective cohort study of women aged 24–48 with PCOS, diagnosed according to 2004 Rotterdam criteria. Participants were grouped by BMI. Quantitative variables were compared by one-way ANOVA and the Tukey method. Analysis for power to detect a difference between means was conducted. Pearson correlation was used to test differences in frequency distribution.

RESULTS: By BMI category, 29 participants were of healthy weight, 11 were overweight, and 11 were obese. HOMA-IR was significantly higher in obese women as compared to overweight and healthy-weight patients (2.88±2.09, 1.13±0.73, 0.84±0.49, respectively; p<0.0001). Moreover, HOMA-%β was significantly increased in obese women as compared to overweight and healthy-weight patients (186.89±131.62, 106.83±46.77, 86.60±40.91, respectively; p<0.0001). Adequate statistical power was not present to distinguish a difference between overweight and normal-weight participants.

A positive linear correlation was found between log HOMA-IR and BMI, and between log HOMA-%β and BMI.

CONCLUSION: Obese PCOS patients have a higher risk of elevated insulin resistance and β-cell function than do those with BMI <30. (J Reprod Med 2016;61:3–10)

Keywords: BMI, body mass index, glucose intolerance, homeostasis, homeostasis model assessment, insulin resistance, obesity, pancreatic β-cell function, polycystic ovary syndrome, waist-to-hip ratio.

The most common endocrinopathy seen in women of reproductive age is polycystic ovary syndrome (PCOS). It is characterized by hyperandrogenism and chronic anovulation, and its prevalence is estimated at 5–10% of reproductive-aged women. Clinical manifestations of PCOS include obesity,
hirsutism, acne, menstrual disorders, insulin resistance (IR), metabolic syndrome, and infertility.\textsuperscript{5,6} PCOS is a collection of signs and features in which no single phenomenon is pathognomonic on its own.\textsuperscript{7} The diagnosis of PCOS is determined either by the 2004 revised Rotterdam consensus criteria\textsuperscript{8,9} or by the National Institutes of Health (NIH) criteria.\textsuperscript{10} Based on these definitions of PCOS, completely different phenotypes with heterogeneous metabolic risk profiles are possible.\textsuperscript{7,11}

Obesity is highly prevalent in PCOS—reaching 67%\textsuperscript{12}—and exacerbates IR and impaired glucose tolerance in women with PCOS.\textsuperscript{13,14} The increased prevalence of obesity in PCOS is associated with an increased prevalence of metabolic syndrome and type 2 diabetes mellitus (T2DM).\textsuperscript{15} Although many women with PCOS are also obese, obesity per se is not one of the diagnostic criteria for PCOS. In fact, it has been established that women who are lean can also have PCOS and metabolic characteristics of the syndrome.\textsuperscript{16}

Insulin resistance, defined as reduced sensitivity or responsiveness to the metabolic actions of insulin, is linked to obesity\textsuperscript{17} and contributes to hyperandrogenism.\textsuperscript{18,19} Despite the fact that the exact pathophysiology of PCOS is unknown, a relationship between IR and PCOS was reported as early as 1980.\textsuperscript{18} Later studies have demonstrated that IR is a key feature in the pathogenesis of PCOS,\textsuperscript{20} with prevalence estimated at 60–79\% independent of obesity.\textsuperscript{21-23} In addition, IR has been found to increase the prevalence of metabolic syndrome \texttimes 11\textsuperscript{fold}\textsuperscript{24,25} and has also been shown to significantly increase the incidence of endothelial dysfunction\textsuperscript{24} and T2DM, all well-established risk factors for cardiovascular disease.\textsuperscript{24,27-29} As IR—generally asymptomatic in its early stages—may lead to impaired glucose tolerance and T2DM, there is great value in identifying women at risk as early as possible. Currently, the management of IR in PCOS includes exercise, weight loss, and insulin sensitizers such as metformin.\textsuperscript{29}

There are various methods used to estimate IR, and each of these methods has advantages and limitations.\textsuperscript{30} The size and type of a study being conducted often dictates the method used, and no single method is necessarily appropriate under all circumstances. The hyperinsulinemic-euglycemic clamp method has been proved to be the gold standard for measuring insulin sensitivity\textsuperscript{30,31} but is not in common use in the clinical setting due to its high cost in dollars, time, and labor\textsuperscript{32} as compared to homeostatic measurements.\textsuperscript{30,33} The homeostasis model assessment (HOMA) method, which was first described in 1985 by Matthews et al,\textsuperscript{34} has been shown to correlate well with the clamp technique and is widely used in clinical and epidemiological research due to its simplicity. This model uses fasting plasma insulin (μU/mL) and fasting plasma glucose (mg/dL) to calculate IR and pancreatic β-cell function (%β) values.

The objectives of our study were threefold. In lean, overweight, and obese groups of women with PCOS we sought to (1) evaluate HOMA measurement of IR and pancreatic β-cell function, (2) compare HOMA-IR and HOMA-%β correlations with body mass index (BMI) and waist-to-hip ratio (WHR), and (3) determine the effect of ethnicity on the predisposition to increased IR and loss of β-cell function.

**Materials and Methods**

We retrospectively studied 51 women with PCOS treated in our center in 2010; the study subjects were 24–48 years old and did not have concomitant thyroid dysfunction, diabetes, hyperprolactinemia, cardiovascular, renal, or hepatic abnormalities, and had not taken any medication that could affect glucose or sex hormone metabolism, such as metformin or hormonal contraceptives, within 3 months of the study.

The study was approved by the Institutional Review Board of St. Luke’s–Roosevelt Hospital Center. Demographic and laboratory data were abstracted from our computerized database. During the clinical examination, height was recorded to the nearest 0.5 cm, and weight was recorded with minimum clothing to the nearest 0.1 kg.

According to BMI, women were grouped as normal weight (BMI 18.5–24.9 kg/m²), overweight (BMI 25–29.9 kg/m²), or obese (BMI ≥30 kg/m²). These same women were also grouped by WHR as obese (WHR ≥0.80) or healthy weight (WHR <0.80).

**Diagnosis of PCOS**

The clinical diagnosis of PCOS was made using the Rotterdam criteria when women had at least 2 of the 3 criteria: ovulatory dysfunction (oligo-ovulation or anovulation), excess androgen activity (hirsutism, acne, or elevated serum androgens), and/or polycystic ovaries viewed by ultrasound.\textsuperscript{10,11}
Oligomenorrhea was defined as <8 menses per year or cycles longer than 35 days in length. Hirsutism was evaluated according to the Ferriman-Gallwey method. Polycystic ovarian morphology was diagnosed using transvaginal ultrasound when at least 1 ovary had ≥12 antral follicles with a mean diameter <10 mm and/or a classic “string of pearls” appearance.

**Biochemical Measurements**

All serum assays were performed by standard procedures after a minimum of an 8-hour fast. Plasma glucose levels were measured using spectrophotometry (Beckman Coulter AU640, Quest Diagnostics, New York, New York). The calibration range of the assay was 10–750 mg/dL with an analytical sensitivity of 10 mg/dL. The intra assay critical values were <40 mg/dL (low) and >500 mg/dL (high).

Plasma insulin was determined using a solid-phase two-site chemiluminescent immunometric assay (Immulite 2000, Quest Diagnostics). The calibration range of the assay was 5–300 μIU/mL with an analytical sensitivity of 5 μIU/mL. The intra assay critical values were 5.5, 4.0, 3.5, 3.9, 3.8, and 3.7% at the levels of 7.67, 12.5, 17.2, 26.4, 100, and 291 μIU/mL, respectively. The corresponding inter assay critical values were 7.3, 4.9, 4.1, 5.0, 4.2, and 5.3%.

Total testosterone (TT) was measured with liquid chromatography and tandem mass spectrometry (LC/MS/MS, Quest Diagnostics). The calibration range of the assay was 2–2000 ng/dL, with an analytical sensitivity of 2 ng/dL. The cross-reaction with 5α-dihydrotestosterone was 2%.

Dehydroepiandrosterone sulfate (DHEAS) was measured with chemiluminescent enzyme immunoassays (Immulite 2000). The calibration range of the DHEAS assay was 0.41–27.14 μmol/L, with an analytical sensitivity of 0.41 μmol/L. No cross-reactivity with other compounds was known.

**Plasma Glucose and Insulin Measurements**

A blood sample was obtained after an 8- to 10-hour fast to measure glucose and insulin levels. Another blood sample for glucose and insulin was obtained 2 hours after an oral intake of 75 g of glucose (Sun-Dex Glucose Tolerance Test Beverage, Fisher Health-Care, Houston, Texas). This oral glucose tolerance test (OGTT) was performed according to the World Health Organization criteria. Normal glucose tolerance was defined as a plasma glucose level <140 mg/dL (7.8 mmol/L) 2 hours after the oral glucose load. Abnormal glucose tolerance was defined as having either impaired glucose tolerance or T2DM. Impaired glucose tolerance was defined as a plasma glucose level of 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.05 mmol/L). Diabetes was defined as a plasma glucose level of ≥200 mg/dL (11.1 mmol/L).

**Calculation of Insulin Resistance and β-Cell Function**

Insulin resistance and β-cell function were measured using the HOMA-IR and β-cell function (HOMA-%β) calculations. HOMA-IR was calculated using the formula HOMA-IR = (fasting insulin μIU/mL × fasting glucose mmol/L)/22.5, and IR was diagnosed when HOMA was >2.67. Insulin levels were considered elevated when they were above the laboratory reference range based on the 95th percentile for the U.S. population, and IR was diagnosed if either fasting insulin was >19 μIU/mL or 2-hours (after 75-g oral glucose) insulin was >79 μIU/mL. HOMA-%β was calculated using the formula

\[ \text{HOMA-%β} = \frac{20 \times \text{fasting insulin μIU/mL}}{\text{glucose mg/dL} – 3.5}. \]

**Statistical Analyses**

All values are expressed as mean ± SD. Quantitative variables were compared by one-way ANOVA (data with normal distribution). Post-hoc tests for homogeneous subsets were performed using the Tukey method. Post-hoc analysis for power to detect a difference between means was conducted (Sample Size Calculator, Decision Support Systems, LP, 2013). Pearson correlation was used to test the differences in frequency distribution. The level of significance in all analyses was set at 5% (p<0.05). Unless otherwise noted, statistical analyses were performed using the SPSS 15.0 software for Windows (SPSS Inc.).

**Results**

**Demographic Characteristics**

Overall, 51 patients participated in the study. According to BMI criteria 57% (29/51) had a healthy weight, 21.5% (11/51) were overweight, and 21.5% (11/51) were obese. No age differences were found between the 3 groups of patients. When stratifying the BMI categories by ethnicity, all Asian patients had normal weight BMI, while the majority of Hispanic patients were obese (Table I).
Laboratory Findings

Fasting insulin was significantly higher in obese women as compared to overweight and healthy-weight patients (14.36±8.68, 5.54±3.26, and 4.34±2.45, respectively; p<0.0001). In addition, fasting glucose was significantly higher in obese women than it was in the other 2 groups (88.00±7.19, 81.54±4.94, and 80.41±5.34, respectively; p<0.003). No differences in fasting insulin and fasting glucose levels were found between healthy-weight and overweight subjects. The 2-hour OGTT insulin and glucose values showed no significant differences among the 3 BMI groups. Moreover, neither TT (62.30±29.43, 60.00±28.97, 63.40±29.18; p=0.96) nor DHEAS (169.66±93.65, 235.30±110.26, 164.18±87.14; p=0.14) levels varied significantly between the healthy-weight, overweight, and obese groups, respectively.

HOMA-IR and HOMA-%β Values Stratified by BMI

As shown in Table II, HOMA-IR was significantly higher in obese women as compared to overweight and healthy-weight patients (2.88±2.09, 1.13±0.73, 0.84±0.49, respectively; p<0.0001). Moreover, as shown in Table III, HOMA-%β was significantly increased in obese women as compared to the other 2 groups (186.89±131.62, 106.83±46.77, 86.60±40.91, respectively; p<0.0001). While no differences in HOMA-IR and HOMA-%β were found between healthy-weight and overweight women, adequate statistical power was not present to distinguish a difference between these groups. A positive linear correlation was found between log HOMA-IR and BMI (Figure 1) and between log HOMA-%β and BMI (Figure 2).

HOMA-IR and HOMA-%β Stratified by WHR

According to the WHR parameters 61% (31/51) of patients had a healthy weight and 39% (20/51) were obese. Table IV illustrates that log (HOMA-IR) was significantly higher in obese women as compared to healthy-weight women (0.53±0.84 and 0.20±0.65, respectively; p<0.002). Table V shows that log (HOMA-%β) was significantly increased in obese women as compared to the healthy-weight group (4.93±0.63 and 4.42±0.51, respectively; p<0.006).

Correlations Between Measures of Obesity and Measures of Metabolic Function

The correlation between HOMA-IR and BMI (r=0.62, p<0.0001) was stronger than that with WHR (0.42, p<0.004) (Figure 2). Similarly, correlation between HOMA-%β and BMI (r=0.54, p<0.0001) was stronger than that between HOMA-%β and WHR (r=0.36, p<0.015).

Discussion

In this study we aimed to evaluate the HOMA methods of computing IR and pancreatic β-cell function in obese, overweight, and healthy-weight women with PCOS. Using the HOMA-IR formula, we found increased insulin resistance in the obese PCOS patient group as compared to the overweight and healthy-weight groups; similarly, our HOMA-%β calculations yielded increased β-cell function in obese PCOS patients as compared to the other

Table I  Race Distribution by BMI Category

<table>
<thead>
<tr>
<th>BMI category</th>
<th>Asian No. (%)*</th>
<th>African-American No. (%)*</th>
<th>Caucasian No. (%)*</th>
<th>Hispanic No. (%)*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight (N=29)</td>
<td>8 (100)</td>
<td>3 (37.5)</td>
<td>16 (59.3)</td>
<td>2 (25.0)</td>
<td>29</td>
</tr>
<tr>
<td>Overweight (N=11)</td>
<td>0 (0)</td>
<td>2 (25)</td>
<td>8 (29.6)</td>
<td>1 (12.5)</td>
<td>11</td>
</tr>
<tr>
<td>Obese (N=11)</td>
<td>0 (0)</td>
<td>3 (37.5)</td>
<td>3 (11.1)</td>
<td>5 (62.5)</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>8</td>
<td>27</td>
<td>8</td>
<td>51</td>
</tr>
</tbody>
</table>
*% within race.

Table II  Mean HOMA-IR by BMI Category

<table>
<thead>
<tr>
<th>BMI</th>
<th>No.</th>
<th>Mean</th>
<th>SD</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5–24.9</td>
<td>29</td>
<td>0.84</td>
<td>0.49</td>
<td>p&lt;0.000</td>
</tr>
<tr>
<td>25–29.9</td>
<td>11</td>
<td>1.13</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>11</td>
<td>2.88</td>
<td>2.09</td>
<td></td>
</tr>
</tbody>
</table>

Table III  Mean HOMA-%β by BMI Category

<table>
<thead>
<tr>
<th>BMI</th>
<th>No.</th>
<th>Mean</th>
<th>SD</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5–24.9</td>
<td>29</td>
<td>86.60</td>
<td>40.91</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>25–29.9</td>
<td>11</td>
<td>106.83</td>
<td>46.77</td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>11</td>
<td>186.89</td>
<td>131.62</td>
<td></td>
</tr>
</tbody>
</table>
2 groups. Neither metabolic parameter appeared elevated in the healthy-weight and the overweight PCOS patient groups; however, the sample size did not allow detection of a statistical difference between the means of those groups. BMI was found to be a better predictor than WHR in detecting insulin resistance and β-cell function. Given the linear relationship between BMI and both log HOMA-%β and log HOMA-IR, we expect a larger sample size to yield a statistically significant difference between the overweight and healthy-weight groups.

Our results that demonstrate increased IR in obese PCOS patients are in agreement with those of Stovall et al. They also found that obese women with PCOS have a greater degree of IR as compared to lean women with PCOS, and that BMI is highly predictive of both insulin and glucose levels in women with PCOS. Further support of our findings comes from Cupisti et al, who found that in PCOS patients, those with BMI ≥25 kg/m² demonstrated more significant changes in endocrine and metabolic parameters, including IR, than did leaner PCOS women. We managed to further stratify the weight distribution among our study population and showed that IR is associated with obesity (BMI ≥30 kg/m²) but not with overweight status (BMI 25–29.9 kg/m²).

In our study population, among different races we found Asian patients with PCOS to be lean, while Hispanic patients with PCOS were more likely to be obese. BMI and WHR were used as measurements to evaluate obesity. Elevated BMI has been described as a risk factor for adverse health consequences, especially among patients with metabolic syndrome or IR. Moreover, BMI has been found to be highly predictive of both insulin and glucose levels in women with PCOS.

With regard to the correlation between BMI and IR in PCOS patients, our findings were different from those of Hurd et al, who concluded that obesity was not an accurate marker for IR in PCOS women. In contrast to our findings of absent IR in

Table IV  Mean Log HOMA-IR by WHR Category

<table>
<thead>
<tr>
<th>WHR</th>
<th>No.</th>
<th>Mean</th>
<th>SD</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.80</td>
<td>31</td>
<td>0.20</td>
<td>0.65</td>
<td>p &lt; 0.002</td>
</tr>
<tr>
<td>≥0.80</td>
<td>20</td>
<td>0.53</td>
<td>0.84</td>
<td></td>
</tr>
</tbody>
</table>

Table V  Mean Log HOMA-%β by WHR Category

<table>
<thead>
<tr>
<th>WHR</th>
<th>No.</th>
<th>Mean</th>
<th>SD</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.80</td>
<td>31</td>
<td>4.42</td>
<td>0.51</td>
<td>p &lt; 0.006</td>
</tr>
<tr>
<td>≥0.80</td>
<td>20</td>
<td>4.93</td>
<td>0.63</td>
<td></td>
</tr>
</tbody>
</table>
lean PCOS women, a recent study in Japan using the HOMA method found that lean PCOS women had IR. One possible explanation for the differences between our findings and those of other studies may be differences in ethnicity. Our study population was ethnically diverse and urban, while other studies might have had a more homogeneous population. A review of the literature demonstrates a relationship between race and the prevalence of insulin resistance. Gue et al found that associations specific for ethnic background were found between BMI, HOMA-IR, and PCOS when comparing Chinese and Dutch Caucasian patients. A BMI of $\geq 30.0$ kg/m$^2$ was associated with a greater incidence of PCOS than was a lower BMI in indigenous women in Australia. Studies conducted in the USA demonstrated greater IR among Mexican-Americans with PCOS as compared to age- and weight-matched non-Hispanic whites. In Japan, 30–40% of young PCOS patients are obese (as compared to the 18% incidence of obesity in their general population), but the incidence of obesity is lower in Japanese PCOS patients than in American and European PCOS patients. Previous studies support our findings that the prevalence of glucose intolerance in Asian PCOS patients appears to be lower than that in non-Asian PCOS patients.

In summary, the extent to which racial background affects the risk of IR in PCOS patients has not been fully determined, but it has been shown that ethnic and racial variations strongly affect the clinical presentation of PCOS in women.

Although the pathophysiology of IR in PCOS is not completely understood, it has been shown that compensatory hyperinsulinism plays an essential role by stimulating androgen synthesis in the thecal cells and decreasing hepatic sex-hormone-binding globulin synthesis in the liver, thereby increasing free androgen availability.

In our study the sample size may have been too small to differentiate androgen levels between healthy-weight, overweight, and obese patients. However, our data may indicate that hyperandrogenism and obesity relate to insulin resistance in a manner that is not completely interdependent.

An alternative mechanism for the pathophysiology of IR in PCOS is a possible post-receptor defect in insulin receptor-mediated cells. Studies on adipocytes, fibroblasts, and skeletal muscles obtained from women with PCOS demonstrated no changes in insulin binding or receptor affinity but did demonstrate decreased tyrosine phosphorylation and increased serine phosphorylation of the insulin receptor. Nestler et al found that insulin-receptor serine phosphorylation, and thereby decreased tyrosine kinase activity, might induce a decrease in glucose transporters.

As discussed previously, IR is known to be a key feature associated with the risk of the metabolic syndrome and the development of T2DM. The urgent need for a simple way of measuring insulin resistance has led to a search for a noninvasive measurement of insulin sensitivity. Several models have been evaluated that are based on fasting insulin and fasting glucose levels and use mathematical calculations to assess insulin sensitivity and pancreatic $\beta$-cell function. Matsuda et al concluded that HOMA is a simple and accurate method for the assessment of insulin sensitivity; it is widely used in the majority of clinical studies. In 2006 Mohlig et al reported that HOMA calculations were a better predictor of IR than fasting insulin by itself, allowing the formula to be utilized in stratified metabolic screening of PCOS patients undergoing OGTT.

In conclusion, we believe that HOMA is a simple and reliable method for identifying IR and the compensatory pancreatic $\beta$-cell function in women with PCOS when stratifying for BMI. Given the evidence of increased IR and $\beta$-cell function with obesity, clinicians should counsel overweight and obese women with PCOS to lose weight to prevent or minimize IR. Special consideration should be given to race in relation to IR. Further studies are needed to assess the extent to which racial background affects the pathogenesis of IR in women with PCOS.

Acknowledgment

The authors wish to acknowledge the writing assistance of Carolyn Waldron, M.S., M.A., departmental medical editor.

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