Use of fasting blood to assess the prevalence of insulin resistance in women with polycystic ovary syndrome

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Objective: To determine the prevalence of insulin resistance (IR) in women with polycystic ovary syndrome (PCOS) using baseline fasting blood measurements of glucose and insulin.

Design: Prospective clinical study.

Setting: Academic endocrinology unit in Palermo, Italy.

Patient(s): Two hundred and sixty-seven women with PCOS, consecutively evaluated, and 50 consecutively selected ovulating controls.

Intervention(s): Fasting blood was obtained for glucose and insulin measurements from all women. For 60 women with PCOS and 20 controls an insulin tolerance test (ITT) was also performed.

Main Outcome Measure(s): Assessment of normal and abnormal values for fasting insulin, glucose/insulin ratio, and the calculated indices of the homeostasis model assessment (HOMA), quantitative sensitivity check index (QUICKI), as well as Kitt (kinetic disappearance of glucose) values after ITT. Evaluation was performed of the ability to detect IR using these methods in obese and nonobese women with PCOS.

Result(s): Normal insulin sensitivity was defined by insulin levels <12 mU/mL, glucose/insulin ratios of <6.4, HOMA values of <47, and QUICKI values of >0.33. In the entire PCOS groups, IR was diagnosed in 65.4% of women using glucose/insulin ratios and in 77% and 79.2% using HOMA and QUICKI. In obese women (body mass index >28 in 48% of group), IR was present in 76.7% as measured by glucose/insulin ratios but was significantly higher (95.3%) using values of either HOMA or QUICKI (P<.01). All indices correlated with Kitt values with QUICKI showing the best correlation.

Conclusion(s): Insulin resistance was detected in approximately 80% of women with PCOS, and in 95% of obese women. The detection of IR is superior using the calculated indices HOMA and QUICKI. (Fertil Steril 2004;82:661–5. ©2004 by American Society for Reproductive Medicine.)

Key Words: Insulin resistance, PCOS, glucose, insulin, HOMA, QUICKI

Polycystic ovary syndrome (PCOS) is considered to be a metabolic disorder (1, 2). However, it remains unclear how frequently the hallmark feature of insulin resistance (IR) can be detected and whether IR is present in all women with the disorder. It is generally assumed that more invasive or provocative testing is necessary to detect IR in most women with PCOS. These tests include the frequently sampled intravenous glucose tolerance test (IV GTT), glycemic clamps, and the insulin tolerance test (ITT) (3–5). All these tests have been shown to correlate well with each other and most recently also with the oral GTT with mathematical modeling (6). Because of the intensity of testing required to assess IR using these measures, only a small number of subjects has been tested (7, 8), and thus these cannot provide reliable data on the prevalence of IR in PCOS. Using the ITT in various ethnic groups, we suggested an overall prevalence of approximately 75% (9).

Although the fasting glucose/insulin (G/I) ratio has been found to correlate well with the frequently sampled IV GTT (10), uncertainty remains as to how well this static measure can identify IR in women with PCOS. It has been suggested that only 50% to 60% of women with PCOS will be found to have IR using the G/I ratio (10, 11).

Other simple indices using basal fasting blood have been suggested to reflect IR bet-
ter than the G/I ratio. In particular, the homeostasis model assessment (HOMA) (12, 13) and the quantitative sensitivity check index (QUICKI) (14) have provided a mathematical means for estimating insulin resistance. The rationale for using these calculations is that the relationships between glucose and insulin reflecting insulin sensitivity are hyperbolic rather than linear (5, 14). Several groups have suggested that linearizing transformations of glucose and insulin would improve the correlation between these mathematical methods and more invasive tests (15, 16); HOMA and QUICKI both have shown a very good correlation with clamp methods (17, 18).

To date, no studies have reported on the prevalence of IR using these techniques in a large group of women with PCOS. Our study assessed insulin sensitivity in 267 consecutively evaluated women with classic features of PCOS by means of several mathematical methods based on basal fasting levels of insulin and glucose. Both lean and obese women with PCOS were evaluated. In a subgroup of these women with PCOS (60 patients), correlations also were sought with the ITT for internal consistency.

**MATERIALS AND METHODS**

Two hundred and sixty-seven women with PCOS who were seen consecutively between 1993 and 2002 were evaluated in the Department of Endocrinology and the Department of Clinical Medicine of the University of Palermo. The diagnosis of PCOS was based on the classic features of hyperandrogenism, chronic anovulation, and the exclusion of Cushing syndrome, tumors, and adrenal enzymatic deficiencies.

Fifty normal ovulatory women, also recruited during this period and evaluated consecutively, served as the controls. The normal women were selected on the basis of having normal body weight, an absence of hirsutism or signs of androgenization, and normal ovulatory menstrual cycles. Presence of normal ovulation was assessed by measurement of serum P (7 ng/mL) on days 22 to 23 of the menstrual cycle.

In all women with PCOS and in normal controls, on two separate days a fasting blood sample was obtained between 8:00 and 9:00 AM for measurements of insulin and glucose. The mean of the two separate samples was used to determine insulin and glucose levels to calculate the G/I ratio, and HOMA and QUICKI values.

In 60 women with PCOS and in 20 normal controls, a modified ITT (insulin 0.1 IU/kg IV) with blood samples for glucose at 0, 3, 6, 9, 12, and 15 minutes was also performed with the calculation of Kitt (kinetic disappearance of glucose) as a measure of IR (19).

Plasma glucose levels were determined by the glucose oxidase technique. Insulin was determined with a double-antibody method using reagents obtained from Linco Research, Inc (St. Charles, MO). Intra-assay and interassay coefficients of variation were <10%. The HOMA and QUICKI scores were calculated according to the following formulas:

\[
\text{HOMA} = \frac{22.5 \times 18}{\text{Fasting insulin} \times \text{Fasting glucose}}
\]

\[
\text{QUICKI} = \frac{1}{\log (\text{Fasting insulin}) + \log (\text{Fasting glucose})}
\]

**RESULTS**

Women with PCOS had a significantly \(P<.01\) higher body mass index (BMI) than controls, although the mean ages were similar (Table 1). Compared with controls, pa-

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (y)</th>
<th>Body mass index</th>
<th>Insulin (μU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>23.8 ± 0.5</td>
<td>22.1 ± 0.3</td>
<td>8.8 ± 0.3</td>
</tr>
<tr>
<td>PCOS</td>
<td>24.3 ± 0.3</td>
<td>27.6 ± 0.4</td>
<td>18 ± 0.5</td>
</tr>
</tbody>
</table>


**TABLE 1**

Mean age, body mass index, and serum insulin (μU/mL) in 287 women with PCOS and in 50 normal weight ovulatory controls.

<table>
<thead>
<tr>
<th>Group</th>
<th>G/I ratio</th>
<th>HOMA</th>
<th>QUICKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>9.5 ± 0.2</td>
<td>31.9 ± 1.0</td>
<td>0.353 ± 0.002</td>
</tr>
<tr>
<td>PCOS</td>
<td>5.5 ± 0.1</td>
<td>68.5 ± 1.5</td>
<td>0.315 ± 0.002</td>
</tr>
</tbody>
</table>


**TABLE 2**

Calculated indices of insulin sensitivity in 287 women with PCOS and in 50 normal weight ovulatory controls.
tients with PCOS had statistically significantly \( (P<.01) \) higher levels of fasting insulin.

The values of the different mathematical models to calculate insulin sensitivity are depicted in Table 2. With all the methods, insulin sensitivity was statistically significantly \( (P<.01) \) lower in women with PCOS than in normal weight controls.

In controls, the normal ranges for serum insulin and insulin sensitivity indices were calculated by mean \( \pm \) 2 standard deviation. Based on 95\% confidence limits, normal limits were as follows: insulin \( <12.1 \, \mu U/mL \), G/I ratio \( >6.4 \), HOMA \( <47 \), and QUICKI \( >.332 \). In the 287 women with PCOS, 87 (33.3\%) had normal fasting insulin levels, 90 (34.5\%) had normal G/I ratios, 60 (23\%) had a normal HOMA index, and 57 (21.8\%) had a normal QUICKI value. Thus, in the entire group of PCOS women, IR was detected in 65.4\% of the women with the G/I ratio, and in 77\% and 79.2\% of women with HOMA and QUICKI scores, respectively. The improved detection of IR by HOMA and QUICKI was of borderline statistical significance.

Fifty-two percent of the women with PCOS were of normal weight (BMI \( <27 \)) \( (18) \), and 48\% of women with PCOS were obese. In the obese patients, normal insulin sensitivity was found in 23.3\% of the patients using the G/I ratio. Normal insulin sensitivity was found significantly less frequently \( (P<.01) \) compared with the G/I ratio (4.7\% of women with either HOMA or QUICKI), suggesting that IR is present in 95.3\% of obese women with PCOS using either HOMA or QUICKI calculations (Table 3, Fig. 1).

The subgroup of women with PCOS and the normal controls who had an ITT were representative (age and BMI) of the controls and the entire group of women with PCOS. Among the women with PCOS in this subgroup, 25 of the 60 were considered obese.

In normal controls, the mean Kitt value was 6.3 \( \pm \) 0.1. The normal range of Kitt values extended down to 4.9, with

### Table 3: Number of women with PCOS with normal insulin resistance parameters.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>Insulin Glucose/insulin ratio</th>
<th>HOMA</th>
<th>QUICKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PCOS</td>
<td>267</td>
<td>33.3%</td>
<td>34.3%</td>
<td>23.0%</td>
</tr>
<tr>
<td>Obese PCOS (BMI ( &gt;28 ))</td>
<td>129</td>
<td>14%</td>
<td>23.3%</td>
<td>4.7*</td>
</tr>
<tr>
<td>Normal weight PCOS (BMI ( &lt;27 ))</td>
<td>138</td>
<td>50%</td>
<td>43.5%</td>
<td>39.1%</td>
</tr>
</tbody>
</table>

Note: BMI = body mass index.

* \( P<.01 \) vs. G/I ratio in obese PCOS. For comparison, of the 60 women with PCOS who underwent ITT testing, only 21.7\% had normal values.


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**Figure 1**

Percentage of 129 obese women with PCOS with IR based on fasting basal insulin (white), G/I ratio (red), HOMA (yellow), or QUICKI (aqua blue). * \( P<.01 \) compared with G/I ratio.

values above this being considered normal; this is consistent with our previous findings (9). Women with PCOS had significantly lower Kitt values (mean 4.3 ± 0.1; \( P < .01 \)). Normal insulin sensitivity using Kitt was found in 13 women with PCOS (21.7%); in only two of the obese patients (8%) and in 11 of the normal-weight women (31%). In the same subgroup of 60 women with PCOS who had an ITT, although 21.7% had normal Kitt values, 45% of women had normal basal insulin, 45% had normal G/I ratios, and 30% had normal HOMA and 22% had normal QUICKI values. Kitt values were similar to HOMA and QUICKI but varied \((P < .05)\) for values of insulin and G/I ratio \((P < .05)\).

All mathematical calculations for determining insulin sensitivity correlated in a statistically significant manner with Kitt (Table 4). However, the best numerical correlation was found using QUICKI \((r = 0.65; P < .01)\).

**TABLE 4**

Correlations of different basal measures to determine insulin resistance with the kinetic decline of blood glucose after the insulin tolerance test (Kitt) in 60 women with PCOS.

<table>
<thead>
<tr>
<th>Basal measure</th>
<th>(r) Value</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin</td>
<td>-0.33</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Glucose/insulin ratio</td>
<td>0.41</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>HOMA</td>
<td>-0.48</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.65</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>


**DISCUSSION**

Most studies on IR in PCOS have been conducted in small groups of patients. This is related, at least in part, to the difficulty and expense of evaluating large groups of women using the more invasive tests. Therefore, more simple methods such as the ITT or G/I ratio have been used, with a reported prevalence of IR between 53% and 75% in women with PCOS (7–9). The largest studies have used a surrogate measure of insulin sensitivity, the simple calculation of G/I ratio (10, 11). In the study by Legro et al. (10) that compared G/I with the frequently sampled IV GTT, only 40 women with PCOS were enrolled, with a suggested prevalence of IR of 53%. Although the G/I ratio has been used widely, HOMA and QUICKI have been reported to be more sensitive measures of IR (12, 13, 16, 17).

In our study, we calculated insulin sensitivity in a large population of women with PCOS using four different methods: basal insulin, G/I ratio, HOMA, and QUICKI. In a subgroup of 60 women with PCOS, we also calculated Kitt values to assess correlations. We chose to compare PCOS patients (with different BMI values) with normal weight controls to determine the overall prevalence of IR by the different methods. (Although obesity clearly increases the rate of IR, comparing PCOS with obese controls addresses the inherent risk of IR in PCOS and already has been addressed in other studies.)

Our data show that IR was detected by HOMA and QUICKI in more patients than it was using basal insulin or the G/I ratio. With these methods, IR may be diagnosed in almost 80% of women with PCOS (77% and 78% for HOMA and QUICKI, respectively). These rates are similar to the observed prevalence in a smaller and heterogeneous population of women with PCOS derived using the ITT (9). Therefore, it appears that the use of simple mathematical methods such as HOMA are probably sufficient to detect IR in patients with PCOS and may substitute for the more expensive and invasive methods.

We observed the improved ability of HOMA and QUICKI to detect IR primarily in the obese group of women with PCOS. Although 23.3% had normal G/I ratios, significantly fewer women, only 4.7%, had normal HOMA and QUICKI values \((P < .01)\). Even fasting insulin levels alone were as beneficial as the G/I ratio. However, HOMA and QUICKI showed only a marginal improvement over the G/I ratio in detecting IR among normal weight women with PCOS: 34.3% for G/I versus 23% and 25.8% for HOMA and QUICKI.

In the past, we showed that variations in mean body weight do not influence the prevalence of insulin resistance in different ethnic populations (9); that study evaluated populations with different diets and genetic backgrounds (American, Italian, and Japanese women). In our present study of an Italian population, the prevalence of IR was similar to our findings in the previous report (9), which also noted a similar degree of IR among different ethnic groups.

In normal weight women, the static measures showed a prevalence of IR of approximately 60%, with the rate with Kitt as 69%. Therefore, with all methods, at least 30% of normal weight women with PCOS appear to have normal insulin sensitivity. This bring up the issue as to whether IR may be truly absent in some nonobese women with PCOS, regardless of the intensiveness of the testing. No study to our knowledge has detected IR in all women with PCOS, regardless of the sophistication of the testing. It has been suggested that milder forms of IR may reduce insulin action only at the level of adipose tissue and not at the level of muscle, which is where IR is reflected using the various methods described (20). An alternative explanation is that IR may truly be absent in a minority of patients with PCOS, allowing the syndrome to evolve without the presence of IR. In the absence of knowledge of the true existence of IR in PCOS, we have not calculated the sensitivity and specificity of using HOMA or QUICKI.

Nevertheless, we have shown that HOMA and QUICKI are sensitive methods for detecting IR in PCOS, suggesting that the overall prevalence of IR in PCOS is approximately 80% when
compared with normal women. Obesity is an important variable contributing to IR, and we have not compared our data with obese controls. The simple mathematical methods used in this study compare favorably with more expensive and time-consuming tests such as the ITT, and may be used for the diagnostic evaluation of IR in women with PCOS.

References
10. Legro RS, Finegood D, Dunai A. A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1998;83:2694–8.