NOTE

Relationship between Homocysteine and Insulin Resistance in Women with Polycystic Ovary Syndrome

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Abstract. Hyperhomocysteinemia is a risk factor for atherosclerotic vascular diseases. It is known that plasma homocysteine levels are higher in polycystic ovary syndrome (PCOS) patients than in healthy subjects. The aim of our study was to determine the relationship between plasma homocysteine level and insulin resistance in women with PCOS. Twenty-nine patients (age, 23.90 ± 5.86 years) and twenty-five healthy subjects (age, 25.24 ± 4.28 years) were involved in the study. Plasma levels of fasting insulin, glucose, homocysteine, FSH, and LH levels were measured. A statistically significant difference in plasma concentrations of HOMA index, homocysteine, basal insulin levels and LH/FSH ratios was observed between groups (P = 0.001, P = 0.001, P = 0.001, and P = 0.01, respectively). There was no relationship between Hcy and the other variables. In multiple logistic regression analysis, age, BMI and insulin resistance were not predictors of Hcy.

Key words: Homocysteine, Polycystic ovary syndrome, Insulin resistance

HOMOCYSTEINE (Hcy) is a sulfur containing amino acid formed during the metabolism of methionine [1]. Classic homocysteinemia has been characterized as the accumulation of Hcy due to defects in enzymatic pathways. Recent research showed that many nonenzymatic factors may influence Hcy levels such as gender, age, nutrition, obesity, smoking, chronic inflammation, physical activity, pregnancy, menstrual cycle, and coffee consumption [2–7].

Elevated plasma Hcy induces endothelial dysfunction and contributes to development of atherosclerotic vascular disease [1]. It has been reported that the Hcy levels are higher in patients with polycystic ovary syndrome (PCOS) than in control subjects, therefore women with PCOS have several cardiovascular disease risk factors [8]. Recently, research has focused on whether plasma Hcy levels were elevated or associated with insulin resistance in women with PCOS [8, 9]. This study was designed to examine the relationship between Hcy and insulin resistance in women with PCOS.

Materials and Methods

All women in our study had spontaneous onset of puberty and normal sexual development since puberty. None of the subjects had taken any medication known to affect carbohydrate metabolism or any hormonal substance for at least 3 months prior to the study. All patients had normal glomerular filtration rates.

PCOS was diagnosed by the following criteria: (1) chronic ovulatory dysfunction, defined as intermenstrual intervals ≥45 days and serum level of progesterone <5 ng/mL on day 21; (2) hyperandrogenemia, defined as a serum level of testosterone greater than the upper normal limit; (3) the presence of bilaterally normal or enlarged ovaries containing at least 7–10 microcysts (<5 mm in diameter) on ultrasonography; and (4) the exclusion of other disorders, such as non-
classic 21-hydroxylase deficiency, congenital adrenal hyperplasia, thyroid dysfunction, Cushing’s syndrome, hyperprolactinemia, impaired glucose tolerance or diabetes that used the medications known to alter insulin secretion or action.

The homeostatic index of insulin resistance was calculated according to the homeostasis model of assessment as follows:

\[
HOMA-IR = \text{fasting insulin (µU/mL) * fasting glucose (mmol/L)/22.5} [10].
\]

The hormone assays were performed on the third day of the menstrual cycle. After 3 days of a standard 300-g carbohydrate diet and a 12-hour overnight fast, fasting insulin and glucose, Hcy, FSH, and LH levels were measured.

Plasma glucose and insulin, FSH, LH, Hcy levels were determined by automatized analyzer and chemiluminescent enzyme immunometric assay method, respectively.

The local ethics committee approved this study, and all the subjects gave their written informed consent.

Data are means (± SD). Statistical analysis was done by using SPSS software, version 7.5 (SPSS, Inc., Chicago, IL). The normality of the distribution of all variables was assessed by the Kolmogorov-Smirnoff test. Differences between two groups in continuous variables that had a normal distribution were evaluated by Student’s t test; for continuous variables that had a skewed distribution, Mann-Whitney U test was used. Pearson’s correlation coefficients were used to calculate correlations between parameters. We used multiple logistic regression analyses to determine associations between Hcy levels and insulin resistance, BMI, and age. \( P<0.05 \) was considered significant.

**Results**

The main characteristics of the patient and the control group are summarized in Table 1. Age and BMI values of the two groups were similar. The mean serum insulin, Hcy, HOMA index and LH/FSH ratios were significantly higher in PCOS women than in controls (Table 1). There was no relationship between Hcy and the other variables (Table 2). We performed stepwise multiple regression analysis using Hcy as the dependent variable. Using this analysis, age, BMI, and insulin resistance were not predictors of Hcy (Table 3).

### Table 1. Demographic, and hormonal characteristics of the patients and control group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 PCOS (n=29)</th>
<th>Group 2 Control (n=25)</th>
<th>Statistical significance</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>23.90 ± 5.86</td>
<td>25.24 ± 4.28</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.30 ± 4.25</td>
<td>23.30 ± 4.12</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>LH/FSH (mIU/mL)</td>
<td>1.44 ± 1.06</td>
<td>0.85 ± 0.42</td>
<td>0.01*</td>
<td></td>
</tr>
<tr>
<td>Basal insulin (mIU/mL)</td>
<td>13.88 ± 8.10</td>
<td>8.06 ± 3.01</td>
<td>0.001*</td>
<td></td>
</tr>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>11.11 ± 5.60</td>
<td>4.26 ± 3.10</td>
<td>0.001*</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>3.21 ± 2.49</td>
<td>1.76 ± 0.73</td>
<td>0.001*</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean and standard deviation. *: Statistically significant

### Table 2. Pearson’s correlations among the variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hcy</th>
<th>Age</th>
<th>IR</th>
<th>LH/FSH</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hcy</td>
<td>—</td>
<td>0.04</td>
<td>0.09</td>
<td>0.20</td>
<td>-0.04</td>
</tr>
<tr>
<td>Age</td>
<td>0.04</td>
<td>—</td>
<td>-0.02</td>
<td>-0.21</td>
<td>0.17</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>0.20</td>
<td>-0.20</td>
<td>0.16</td>
<td>—</td>
<td>-0.04</td>
</tr>
<tr>
<td>IR</td>
<td>0.09</td>
<td>-0.02</td>
<td>—</td>
<td>0.16</td>
<td>0.2</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.04</td>
<td>0.17</td>
<td>0.20</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*: Statistically significant

### Table 3. Multiple regression analysis with Hcy as the dependent variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>t</th>
<th>Significant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>S.E</td>
<td>Beta</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.41</td>
<td>0.25</td>
<td>-0.31</td>
<td>-1.66</td>
</tr>
<tr>
<td>Age</td>
<td>0.21</td>
<td>0.18</td>
<td>0.22</td>
<td>1.13</td>
</tr>
<tr>
<td>IR</td>
<td>-0.14</td>
<td>0.43</td>
<td>-0.06</td>
<td>-0.32</td>
</tr>
</tbody>
</table>
**Discussion**

In the present study, we found that Hcy levels were higher in women with PCOS than in healthy women although the mean Hcy levels were within the normal range, which was consistent with the previous report by Loverro et al. [8]. However, increased circulating levels of Hcy were not correlated with insulin resistance in our study.

We know that women with PCOS have several cardiovascular disease risk factors. The relation of hyperinsulinemia and hyperhomocysteinemia in cardiovascular diseases has been demonstrated by several studies [11–16], but in women with PCOS whether plasma Hcy levels are associated with insulin resistance is still debated [8–9].

Giltay et al. [17] demonstrated that high insulin levels were associated with increased plasma Hcy levels in healthy, nonobese women. Laivuori et al. [18] suggested that there was relation between insulin resistance and elevated Hcy in pregnant women with pre-eclampsia. Yarali et al. [19] showed that Hcy was significantly elevated in PCOS patients as related to insulin resistance. On the other hand, Sills et al. [20] did not determine any association between plasma Hcy and insulin levels in women with PCOS.

Although Rosolova et al. found that an unexpected inverse relationship existed between insulin resistance and serum Hcy in healthy subjects [21], Schachter et al. reported that insulin resistance in patients with PCOS is associated with elevated plasma Hcy [9].

On the other hand, it has been reported that insulin resistance, and plasma Hcy levels were correlated with age, and obesity [5]. In the present study, age and BMI values of the two groups were similar. We did not determine relationship among the variables.

In conclusion, we found that there was no a relationship between plasma Hcy levels and insulin resistance in women with PCOS. Therefore, we suggest that plasma Hcy levels are elevated with an independent mechanism from insulin resistance in PCOS women and, insulin resistance is not a predictor of Hcy.

**References**


