Indices of low-grade chronic inflammation in polycystic ovary syndrome and the beneficial effect of metformin

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BACKGROUND: Women with polycystic ovary syndrome (PCOS) have an increased prevalence of insulin resistance (IR) and related disorders. Elevated serum levels of cellular adhesion molecules (CAMs) reflect low-grade chronic inflammation and have been associated with several insulin-resistant states. The objective of this study is to investigate whether soluble inflammatory markers [soluble intercellular adhesion molecule-1 (sICAM-1), soluble endothelial leukocyte adhesion molecule-1 (sE-selectin), soluble vascular cell adhesion molecule-1 (sVCAM-1) and C-reactive protein (CRP)] are altered in PCOS and to further elucidate the effect of metformin treatment on their levels.

METHODS: Two young populations were studied [62 women with PCOS and 45 normal women of similar age, BMI and waist-to-hip ratio (WHR)]. Plasma levels of sICAM-1, sVCAM-1, sE-selectin and high-sensitivity CRP (hsCRP) were measured in both groups. Additionally, the effect of metformin on these molecules was investigated in 22 women with PCOS who accepted to metformin protocol (1700 mg daily for a 6-month period). RESULTS: In the total population studied, plasma levels of hsCRP (mg/l), sICAM-1 (ng/ml) and sE-selectin (ng/ml) were higher in the PCOS group compared with those in controls (hsCRP 1.31 ± 0.22 versus 0.92 ± 0.27, P = 0.014, sICAM-1 301.21 ± 24.80 versus 209.86 ± 17.05, P = 0.025, sE-selectin 57.37 ± 4.08 versus 45.67 ± 4.62, P = 0.045, respectively). sVCAM-1 (ng/ml) did not differ statistically among the two groups (P = 0.896). A significant reduction in hsCRP and sVCAM-1 was achieved after 6 months of metformin administration: PCOS pretreatment hsCRP 1.92 ± 0.60 versus PCOS post-treatment hsCRP 0.52 ± 0.26, P = 0.005; PCOS pretreatment sVCAM-1 365.82 ± 99.77, P = 0.039. CONCLUSION: These findings imply the presence of chronic inflammation in women with PCOS. Metformin decreases the levels of plasma inflammatory indices. Further investigation is required to determine whether these findings may prove to be of clinical significance for PCOS patients.

Key words: cellular adhesion molecules/inflammation/insulin resistance/metformin/PCOS

Introduction

Polycystic ovary syndrome (PCOS), probably the most common endocrinopathy of reproductive age (Diamanti-Kandarakis et al., 1999), which is characterized by anovulation, hyperandrogenaemia and, frequently, insulin resistance (IR) represents a disorder with increased risk for type 2 diabetes (T2D) (Ehrmann et al., 1999; Orio et al., 2004).

PCOS is associated with obesity, metabolic aberrations (Dunaif, 1997; Ehrmann et al., 1999) and surrogate markers of cardiovascular disease (Talbott et al., 1995; Christian et al., 2003) such as dyslipidaemia (Dunaif, 1997; Ovalle and Azziz, 2002; Orio et al., 2004), increased serum levels of plasminogen activator inhibitor-1 (PAI-1) (Diamanti-Kandarakis et al., 2004), elevated serum levels of C-reactive protein (CRP) (Boulman et al., 2004; Talbott et al., 2004), elevated plasma levels of advanced glycation end-product (AGEs) (Diamanti-Kandarakis et al., 2005a), increased endothelin-1 levels (Diamanti-Kandarakis et al., 2001), endothelial dysfunction (Paradisi et al., 2001; Diamanti-Kandarakis et al., 2005b) and echocardiographic abnormalities (Tiras et al., 1999). These factors are known to contribute to atherogenesis and chronic inflammation (Alexander, 1994; Wilson et al., 1999; Lee et al., 2001; Pai et al., 2004).

The levels of CRP and cellular adhesion molecules (CAMs) [soluble intercellular adhesion molecule-1 (sICAM-1), soluble
vascular cell adhesion molecule-1 (sVCAM-1) and soluble endothelial leukocyte adhesion molecule-1 (sE-selectin) in serum reflect low-grade inflammation of the endothelium and predict independently coronary heart disease and T2D (Kado and Nagata, 1999; Ley and Hoo, 2001; Kowalska et al., 2002; Roldan et al., 2003; Corti et al., 2004; Meigs et al., 2004; Pai et al., 2004). However, their presence in PCOS has not been confirmed (Kelly et al., 2001; Hammadeh et al., 2003; Bahceci et al., 2004; Boulman et al., 2004; Mohlig et al., 2004; Nasiek et al., 2004; Talbott et al., 2004; Tarkun et al., 2004; Bickerton et al., 2005).

Efforts to prevent or to decrease the serum levels of these risk factors could be justified. Insulin-lowering agents such as metformin have been shown to lower traditional cardiovascular risk factors (Nagi and Yudkin, 1993; Grant, 1996; Mather et al., 2001; Chu et al., 2002). In addition, metformin’s use has been associated with a favourable effect on insulin sensitivity, hyperandrogenism, menstrual pattern and ovulatory function in obese and non-obese women with PCOS (Velazquez et al., 1994; Nestler and Jakubowicz, 1997; Diamanti-Kandarakis et al., 1998; Morin-Papunen et al., 1998; UKPDS, 1998). Recently, metformin has been associated with a significant decrease in serum CRP levels in PCOS women, but not all authors have agreed upon this (Morin-Papunen et al., 2003; Mohlig et al., 2004).

The aim of this study was to investigate whether the soluble inflammatory markers (sICAM-1, sE-selectin, sVCAM-1 and CRP) are altered in PCOS and to further elucidate the effect of metformin treatment on their levels.

Materials and methods

One hundred and seven Greek Caucasian women were studied: 62 patients with PCOS and 45 normal women with normal androgen levels and regular menstrual cycles (every 28–30 ± 2 days).

Each patient with PCOS met diagnostic criteria for PCOS based on the Rotterdam criteria (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Hyperandrogenaemia was assessed as total testosterone levels above the 95th percentile of the levels detected in a group of normal menstruating women with normal cycles and, clinically, by the presence of hirsutism and acne. Chronic anovulation was assessed as oligomenorrhoea, i.e. less than eight cycles per year. To rule out congenital adrenal hyperplasia, we conducted a Synacthen test in each woman with a basal 17-hydroxyprogesterone (17-OHP) plasma level ≥1.5 ng/ml.

The enrolled population was clinically healthy and not suffering from chronic or acute disease. Oral contraceptives or other drugs that could interfere with the hormonal and metabolic studies, if administrated, were discontinued for at least 3 months before the study.

Inclusion criteria were Rotterdam criteria for the PCOS population and exclusion of PCOS features in control group. Among exclusion criteria were smoking, intense physical activity, loss of weight the last 3–6 months, impaired fasting glucose in the PCOS population and control group. Women in the control group with abnormal ovarian morphology were also excluded.

Regarding their eating habits, women were asked to follow a regular weight-maintaining diet according to dietician’s instructions for 3 months before participation in the study.

Weight, height and waist and hip circumferences were measured. Waist circumference was obtained as the smallest circumference at the level of the umbilicus. Hip circumference was obtained as the widest circumference at the level of the buttocks. Body weight was measured using analogue scales in light clothing; height was measured barefoot using a stadiometer. BMI (kg/m²) was calculated to assess obesity and waist-to-hip ratio (WHR) to assess body fat distribution.

Ovarian morphology was assessed in all subjects (by the same operator) by transabdominal ultrasound, and Adams’s criteria were used to define it (Adams et al., 1985).

All women recruited were studied during the follicular phase of their menstrual cycle. In the amenorrhoeic women, recent ovulation was excluded by progesterone measurement (<5 nmol/l). Physical examination was performed in each person by two doctors.

The protocol was approved by the Institutional Review Committee of Laiko General Hospital, and written informed consent was obtained from each subject before entry into the study.

Blood samples were collected from all patients and healthy controls between 08:00 and 10:00 hours, after an overnight fast. They were centrifuged immediately, and serum was stored at −80°C until assayed for glucose (GLU), insulin (INS), total cholesterol (TC), total testosterone (TT), sex hormone-binding globulin (SHBG), free testosterone (fT), androstenedione (Δ4A), LH, FSH, 17-OHP, dehydroepiandrosterone sulphate (DHEAS), high-sensitivity CRP (hsCRP), sICAM-1, sVCAM-1 and sE-selectin. All measurements were performed using the ChemWell® Analyzer (Awareness Technology, Palm City, FL, USA), unless otherwise stated.

Synacthen test was performed using Synacthene 0.25 mg/ml (Novartis Pharma SA, Rueil-Malmaison, France).

Plasma fasting glucose (mg/dl) was determined by the glucose oxidase colour method (Glucose LR, GOD-PAP; Linear Chemicals, Barcelona, Spain). TC (mg/dl) was determined by the enzymatic Cobas Mira method (Cholesterol LR, CHOD-PAP; Linear Chemicals). Insulin (µU/ml) was measured by a solid-phase enzyme-amplified sensitivity immunoassay (INS-EASIA; Biosource Technologies, Nivelles, Belgium).

Total testosterone (ng/dl) was measured by enzyme-linked immunosorbent assay (ELISA) (testosterone enzyme immunoassay test kit, LI7603; Linear Chemicals). SHBG serum levels (nmol/l) were measured by ELISA (SHBG ELISA, MX 520 11; IBL, Hamburg, Germany). Plasma samples were analysed for free testosterone (pg/ml) using the commercially available Coat-A-Count FT Kit (Diagnostic Products, Los Angeles, CA, USA). DHEA-S (ng/ml) serum levels were measured by DSL DHEA-S radioimmunoassay kit (Diagnostic Systems Laboratories, Webster, TX, USA). LH (IU/l) and FSH (IU/l) were measured using the LHsp and FSH IRMA kits from Biosource Technologies. Δ4A (ng/ml) was measured by radioimmunoassay using active androstenedione-coated tube radioimmunoassay kit DSL 3800 (Diagnostic Systems Laboratories).

The intra- and inter-assay coefficients of variation (CVs) for low and high levels, respectively, were (a) 3.0% and 5.3% and 4.5% and 9.5%, for insulin, (b) 5.0 and 6.4% and 4.4 and 8.4%, for total testosterone, (c) 4.3 and 5.5% and 3.2 and 3.4%, for free testosterone, (d) 3.0 and 5.3% and 7.2 and 8.4%, for SHBG, (e) 6.5 and 8.8% and 3.5 and 4.5%, for LH, (f) 2.7 and 5.3% and 1.6 and 3.6%, for FSH, (g) 9.4 and 6.3% and 9.6 and 9.9%, for DHEA-S, and (h) 5.6 and 2.8% and 9.8 and 7.0%, for Δ4A.

hsCRP (mg/l) levels were determined by ELISA (high-sensitivity CRP enzyme immunoassay test kit, LI7500; Linear Chemicals). sICAM-1 (ng/ml) plasma levels were determined by ELISA (sICAM-1 ELISA kit, Diaclone Research, Besancon, France). sVCAM-1 (ng/ml) plasma levels were determined by ELISA (sVCAM-1 ELISA kit, Diaclone Research). The intra- and inter-assay CVs for low and high levels were, respectively, (a) 7.5 and 4.1% and 2.3 and 2.5%, for hsCRP, (b) 2.82 and 8.15% and 1.03 and 3.93%, for sICAM-1, and (c) 2.27 and 5.94% and 0.45 and 1.44%, for sVCAM-1. Plasma sE-selectin
levels were determined by enzyme immunoassay technique (R&D Systems, Minneapolis, MN, USA), with intra-assay CVs of 4.7 and 5% for low and high control samples and inter-assay CVs of 5.7 and 8.8% for low and high control samples, respectively.

IR was estimated by the quantitative insulin sensitivity check index (QUICKI).

QUICKI is defined as: QUICKI = 1/log (fasting insulin) + log (fasting glucose) (Katz et al., 2000).

Twenty-two women with PCOS accepted to participate in the metformin protocol. They received a dose of 1700 mg of metformin daily for a 6-month period (850 mg twice daily) (Lhipa Sante; Aron Medicia Division, Lyon, France). Initially, metformin was administered in incremental doses [i.e. 850/2 mg, 850 mg, (850 + 850/2) mg, 1700 mg] every 7 days until the final dose of 1700 mg daily. All women were urged to maintain the same diet followed before treatment and were checked monthly. No severe side effects were reported during the study. After 6 months of treatment, they were reevaluated clinically, biochemically and hormonally.

Continuous variables are presented as mean ± SE. Continuous variables were assessed for normal distribution graphically and by the nonparametric Kolmogorov–Smirnov test. Variables with asymmetric distribution were log transformed or analysed by nonparametric statistical tests.

Differences among continuous variables between the two groups (PCOS versus controls) were evaluated using two-sided Student’s unpaired t-test or Mann–Whitney U-test for asymmetric variables. Analysis of covariance was used to evaluate statistical significance of differences between PCOS and controls after adjusting for BMI.

Differences among continuous variables before and after treatment were assessed by two-sided Student’s paired t-test or Wilcoxon test for asymmetric variables. General linear models for repeated measurements were used to assess the differences between baseline and post-metformin values, by using BMI change as a covariate.

Multiple regression analysis was performed in the total population for each inflammatory index separately considered as dependent variables and independent variables: GROUP (PCOS–control), total testosterone (TT), SHBG, BMI and QUICKI. A second multiple regression analysis was performed in the PCOS population for each inflammatory index separately considered as dependent variables and as independent variables: TT, SHBG, BMI and QUICKI.

Categorical variables were assessed by chi-square test. P < 0.05 was considered to represent statistical significance. The analysis was performed using Statistical Package for the Social Sciences (SPSS) version 11.01 (SPSS, Chicago, IL, USA) for Windows XP.

Results

Anthropometric characteristics and the main hormonal and metabolic profile of PCOS patients and normal women are listed in Table I.

hsCRP, sICAM-1 and sE-selectin levels were significantly lower in the controls compared with the PCOS group. The levels of sVCAM-1 did not differ statistically between the two groups (Table I).

hsCRP was positively related to BMI (r = 0.575, P < 0.001) and sICAM-1 (r = 0.297, P = 0.021) and negatively to Δ4A (r = −0.388, P = 0.010) and DHEA-S (r = −0.392, P = 0.020), sICAM-1 was positively related to age (r = 0.294, P = 0.021) and BMI (r = 0.419, P = 0.001) (Table II).

The baseline values of sICAM-1 and sE-selectin were higher in the treated PCOS patients compared with the untreated PCOS patients: sICAM-1, 388 ± 47 versus 254 ± 26 ng/ml, P = 0.01; and sE-selectin, 73 ± 36 versus 47 ± 24 ng/ml, P = 0.005, respectively. Treated PCOS women also had higher baseline LH than the untreated PCOS women (9.8 ± 5.7 versus 6.9 ± 2.9 IU/l, P = 0.048, respectively). All other anthropometric, hormonal and metabolic characteristics did not differ significantly between the two PCOS subgroups.

By using BMI change as a covariate, general linear models for repeated measurements were used to assess the differences between baseline and post-metformin administration values. After adjustment for BMI change, sVCAM-1 and hsCRP were significantly decreased (P = 0.039 and P = 0.005, respectively). Results at baseline and after 6 months of metformin treatment are summarized in Table III.

In multiple regression analysis for the total population, PCOS presence and BMI were predictors of sICAM-1, soluble endothelial leukocyte adhesion molecule-1; SHBG, sex hormone-binding globulin; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell; TC, total cholesterol; TT, total testosterone; WHR, waist-to-hip ratio; Δ4A, free testosterone androstenedione.

Comparison of means (±SE) for the measured parameters between PCOS and control groups and statistical significance of the differences. Data are given means ± SE, P<0.05 statistically significant; conversion factors for SI units are as follows: TT, nmol/l = ng/dl x 0.0347; fT, pmol/l = pg/ml x 3.467; DHEAS, nmol/l = ng/ml x 3.47; Δ4A, nmol/l = ng/ml x 3.49; GLU, μmol/l = mg/dl x 0.0555; INS, pmol/l = μU/ml x 7.175; TC, mmol/l = mg/dl x 0.02586. CRP, C-reactive protein; DHEA-S, dehydroepiandrosterone sulphate; TT, free testosterone; GLU, glucose; INS, insulin; QUICKI, quantitative insulin sensitivity check index; sE-selectin, soluble endothelial leukocyte adhesion molecule-1; SHBG, sex hormone-binding globulin; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell; TC, total cholesterol; TT, total testosterone; WHR, waist-to-hip ratio; Δ4A, free testosterone androstenedione.

Table I. Anthropometric characteristics, main hormonal and metabolic profile as well as levels of inflammatory markers in polycystic ovary syndrome (PCOS) patients and normal women

<table>
<thead>
<tr>
<th>Study group</th>
<th>PCOS (n = 62)</th>
<th>Controls (n = 45)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24.3 ± 0.61</td>
<td>25.89 ± 0.61</td>
<td>0.080</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4 ± 0.90</td>
<td>25.03 ± 0.91</td>
<td>0.074</td>
</tr>
<tr>
<td>HCR</td>
<td>0.79 ± 0.14</td>
<td>0.75 ± 0.11</td>
<td>0.100</td>
</tr>
<tr>
<td>TT (ng/dl)</td>
<td>100.21 ± 3.53</td>
<td>38.33 ± 2.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>fT (pg/ml)</td>
<td>3.41 ± 0.18</td>
<td>2.25 ± 0.28</td>
<td>0.002</td>
</tr>
<tr>
<td>DHEA-S (ng/ml)</td>
<td>2664.11 ± 208.02</td>
<td>2385.08 ± 300.12</td>
<td>0.475</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>35.07 ± 3.19</td>
<td>42.57 ± 2.24</td>
<td>0.090</td>
</tr>
<tr>
<td>Δ4A (ng/ml)</td>
<td>3.06 ± 0.16</td>
<td>1.62 ± 0.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td>8.20 ± 0.67</td>
<td>6.08 ± 0.39</td>
<td>0.009</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>5.03 ± 0.22</td>
<td>6.01 ± 0.64</td>
<td>0.077</td>
</tr>
<tr>
<td>GLU (mg/dl)</td>
<td>92.73 ± 2.40</td>
<td>84.86 ± 1.96</td>
<td>0.019</td>
</tr>
<tr>
<td>INS (μU/ml)</td>
<td>14.45 ± 1.73</td>
<td>8.44 ± 0.73</td>
<td>0.001</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>183.18 ± 8.74</td>
<td>168.81 ± 6.68</td>
<td>0.215</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.334 ± 0.004</td>
<td>0.362 ± 0.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sICAM-1 (ng/ml)</td>
<td>301.21 ± 24.80</td>
<td>209.86 ± 17.05</td>
<td>0.003</td>
</tr>
<tr>
<td>sE-selectin (ng/ml)</td>
<td>57.37 ± 4.08</td>
<td>45.67 ± 4.62</td>
<td>0.022</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>1.31 ± 0.22</td>
<td>0.92 ± 0.27</td>
<td>0.005</td>
</tr>
<tr>
<td>sVCAM-1 (ng/ml)</td>
<td>547.10 ± 66.96</td>
<td>524.95 ± 74.45</td>
<td>0.980</td>
</tr>
</tbody>
</table>
Table II. Results from correlation analysis for adhesion molecules

<table>
<thead>
<tr>
<th>Variable</th>
<th>Spearman’s coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>0.20</td>
<td>0.04</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>0.26</td>
<td>0.009</td>
</tr>
<tr>
<td>QUICKI</td>
<td>-0.24</td>
<td>0.01</td>
</tr>
<tr>
<td>INS</td>
<td>0.25</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>0.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHR</td>
<td>0.38</td>
<td>0.009</td>
</tr>
<tr>
<td>sSE-selectin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sICAM-1</td>
<td>0.21</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI</td>
<td>0.32</td>
<td>0.001</td>
</tr>
<tr>
<td>sICAM-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sSE-selectin</td>
<td>0.21</td>
<td>0.03</td>
</tr>
<tr>
<td>CRP</td>
<td>0.26</td>
<td>0.009</td>
</tr>
<tr>
<td>BMI</td>
<td>0.36</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P < 0.05 statistically significant.

CRP, C-reactive protein; INS, insulin; QUICKI, quantitative insulin sensitivity check index; sE-selectin, soluble endothelial leukocyte adhesion molecule-1; sICAM-1, soluble intercellular adhesion molecule-1; TT, total testosterone; WHR, waist-to-hip ratio.

Table III. Comparison of measured parameters (mean ± SE) before and after metformin treatment and statistical significance of the differences

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean value ± SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td></td>
</tr>
<tr>
<td>BMI (Kg/m²²)</td>
<td>30.65 ± 1.40</td>
<td>28.75 ± 2.09</td>
</tr>
<tr>
<td>WHR</td>
<td>0.79 ± 0.03</td>
<td>0.80 ± 0.02</td>
</tr>
<tr>
<td>TT (ng/dl)</td>
<td>91.82 ± 8.07</td>
<td>81.39 ± 10.94</td>
</tr>
<tr>
<td>Free testosterone (μg/ml)</td>
<td>3.48 ± 0.28</td>
<td>2.71 ± 0.30</td>
</tr>
<tr>
<td>Δ4A (ng/ml)</td>
<td>3.31 ± 0.26</td>
<td>2.39 ± 0.18</td>
</tr>
<tr>
<td>DHEA-S (ng/ml)</td>
<td>3052.54 ± 281.27</td>
<td>2632.76 ± 364.62</td>
</tr>
<tr>
<td>GLU (mg/dl)</td>
<td>89.33 ± 5.86</td>
<td>70.92 ± 8.74</td>
</tr>
<tr>
<td>INS (μU/ml)</td>
<td>17.30 ± 3.99</td>
<td>14.52 ± 3.60</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>1.92 ± 0.60</td>
<td>0.52 ± 0.26</td>
</tr>
<tr>
<td>sICAM-1 (ng/ml)</td>
<td>391.55 ± 49.52</td>
<td>367.89 ± 56.52</td>
</tr>
<tr>
<td>sVCAM-1 (ng/ml)</td>
<td>668.09 ± 98.38</td>
<td>365.82 ± 99.77</td>
</tr>
<tr>
<td>sE-selectin (ng/ml)</td>
<td>72.81 ± 8.13</td>
<td>77.17 ± 8.94</td>
</tr>
</tbody>
</table>

Data are given means ± SE, P < 0.05 statistically significant; conversion factors for SI units are as follows: TT, nmol/l = ng/dl × 0.0347; FT, pmol/l = pg/ml × 3.467; DHEAS, nmol/l = ng/ml × 3.47; Δ4A, nmol/l = ng/ml × 4.9; GLU, mmol/l = mg/dl × 0.0555; INS, pmol/l = μU/ml × 7.175.

Discussion

In this study, it has been demonstrated that chronic inflammatory markers (hsCRP, sICAM-1 and sE-selectin) are elevated in women with PCOS compared with controls and that a 6-month treatment with metformin had a statistically significant beneficial effect on hsCRP and sVCAM-1.

In the last decade, markers of low-grade inflammation and certain components of the haemostatic system have been found to predict atherosclerotic risk (Ridker et al., 2000; Danesh et al., 2004) in IR states such as metabolic syndrome and T2D.

PCOS is characterized by hyperandrogenaemia and chronic anovulation and has been associated with metabolic aberrations. It has been suggested that it represents a female subtype of metabolic syndrome (Sam and Dunaif, 2003), carrying a potential pre-atherogenic load. Evidence of low-grade inflammatory infiltration in PCOS is indicated by the presence of several elevated markers such as CRP levels (Kelly et al., 2001; Boullon et al., 2004; Tarkun et al., 2004), inflammatory cytokines [i.e. interleukin-6 (IL-6) and IL-18] (Escobar-Morreale et al., 2003, 2004) and increased leukocyte count (Orio et al., 2005). In this study, the presence of elevated levels of CAMs provides further evidence supporting this notion. The increased hsCRP levels in women with PCOS are in line with those in most published data; however, contradictory data have been published (Mohlig et al., 2004; Bickerton et al., 2005). CRP has been established as an independent cardiovascular risk factor, and its presence in this group of young women with PCOS is confirmed. The combination of elevated adhesion molecules and hsCRP in these young women, who did not suffer from overt hyperglycaemia, T2D or cardiovascular disease (CVD), may have an adverse additive effect on their cardiovascular profile (Kado and Nagata, 1999; Cybulsky et al., 2001; Ley and Hoo, 2001; Targher et al., 2001; Bluher et al., 2002; Kowalska et al., 2002; Leinonen et al., 2003; Rollan et al., 2003; Boulou et al., 2004; Corti et al., 2004; Meigs et al., 2004; Pai et al., 2004).

Although genetic abnormalities such as polymorphisms in inflammatory markers have been identified in hyperandrogenic states, the relationship between hyperandrogenaemia and inflammation is not clarified (Escobar-Morreale et al., 2004; Peral et al., 2002; Villuendas et al., 2002; Escobar-Morreale et al., 2003). In this study, the positive correlation between hsCRP concentrations and hyperandrogenaemia and the predictive value of PCOS presence revealed by regression analysis on sICAM and sE-selectin levels may prove to be of some clinical relevance.

A significant reduction in sVCAM-1 and hsCRP was achieved after 6 months of metformin administration, an effect independent of BMI. CRP and VCAM-1 have been implicated as major contributors in atherogenic processes, and metformin administration therefore seems to have additional beneficial effects on the atherogenic profile of PCOS patients (Ridker et al., 2000, 2003; Ley and Hoo, 2001; Hansson, 2005). However, the differential effect of metformin on plasma concentrations of sICAM-1 and sE-selectin cannot be explained in this study; it is possible that longer duration of treatment is required, as it has been shown in PCOS and other IR populations (Morin-Papunen et al., 1998; UKPDS, 1998; Caballero, 2003; Grant, 2003; Mampetu et al., 2003; Morin-Papunen et al., 2003; Caballero et al., 2004).

Among the limitations of this study is the fact that oral glucose tolerance test was not performed, and it is possible that women with impaired glucose tolerance but with normal fasting glucose have not been excluded. Another limitation is the difference in sICAM and sE-selectin cannot be explained in this study; it is possible that longer duration of treatment is required, as it has been shown in PCOS and other IR populations.

The reliability of the data, derived from young PCOS women, suggest a pro-atherogenic state, reflected by the presence of inflammatory markers on which metformin is shown to have a beneficial effect.

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References


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