The effect of diet and exercise on markers of endothelial function in overweight and obese women with polycystic ovary syndrome

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Submitted on November 28, 2011; resubmitted on March 9, 2012; accepted on March 22, 2012

BACKGROUND: Women with polycystic ovary syndrome (PCOS) present with vascular abnormalities, including elevated markers of endothelial dysfunction. There is limited evidence for the effect of lifestyle modification and weight loss on these markers. The aim of this study was to determine if 20 weeks of a high-protein energy-restricted diet with or without exercise in women with PCOS could improve endothelial function.

METHODS: This is a secondary analysis of a subset of 50 overweight/obese women with PCOS (age: 30.3 ± 6.3 years; BMI: 36.5 ± 5.7 kg/m²) from a previous study. Participants were randomly assigned by computer generation to one of three 20-week interventions: diet only (DO; n = 14, ≈ 6000 kJ/day), diet and aerobic exercise (DA; n = 16, ≈ 6000 kJ/day and five walking sessions/week) and diet and combined aerobic-resistance exercise (DC; n = 20, ≈ 6000 kJ/day, three walking and two strength sessions/week). At Weeks 0 and 20, weight, markers of endothelial function [vascular cell adhesion molecule-1 (sVCAM-1), inter-cellular adhesion molecule-1 (sICAM-1), plasminogen activator inhibitor-1 (PAI-1) and asymmetric dimethylarginine (ADMA)], insulin resistance and hormonal profile were assessed.

RESULTS: All three treatments resulted in significant weight loss (DO 7.9 ± 1.2%, DA 11.0 ± 1.6%, DC 8.8 ± 1.1; P < 0.001 for time; P = 0.6 time × treatment). sVCAM-1, sICAM-1 and PAI-1 levels decreased with weight loss (P ≤ 0.01), with no differences between treatments (P ≥ 0.4). ADMA levels did not change significantly (P = 0.06). Testosterone, sex hormone-binding globulin and the free androgen index (FAI) and insulin resistance also improved (P < 0.001) with no differences between treatments (P ≥ 0.2). Reductions in sVCAM-1 were correlated to reductions in testosterone (r = 0.32, P = 0.03) and FAI (r = 0.33, P = 0.02) as well as weight loss (r = 0.44, P = 0.002). Weight loss was also associated with reductions in sICAM-1 (r = 0.37, P = 0.008).

CONCLUSIONS: Exercise training provided no additional benefit to following a high-protein, hypocaloric diet on markers of endothelial function in overweight/obese women with PCOS.

Clinical Trials Registration Number: ACTRN12606000198527.

Key words: polycystic ovary syndrome / endothelial / vascular / cardiovascular / diet

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, presenting in 8–18% of this population (Norman et al., 2007; March et al., 2010). PCOS is associated with a number of reproductive disorders and is characterized by the presence of polycystic ovaries, menstrual dysfunction, infertility and hyperandrogenism. PCOS also increases the prevalence and risk of cardiovascular disturbances including insulin resistance, hypertension and dyslipidaemia (Norman et al., 2007; Wild et al., 2010), which impact negatively on the long-term health and leads to the development of cardiovascular disease (CVD).

Women with PCOS present with vascular abnormalities including endothelial dysfunction (Paradisi et al., 2001; Diamanti-Kandarakis...
Palomba, hydrogenism and CVD risk markers in overweight women with PCOS.

Eating alone for improving insulin sensitivity and reducing abdominal fat in overweight women with PCOS has been shown to predict the development of CVD (Moran et al., 2001) and have been shown to predict the development of CVD (Moran et al., 2001). Endothelial dysfunction is an early feature of atherosclerosis and plays an important role in the development of atherosclerotic diseases. Endothelial function can be investigated by measuring circulating markers, produced by the endothelium, such as asymmetric dimethylarginine (ADMA), an endogenous competitive inhibitor of nitric oxide (NO) synthase; plasminogen activator inhibitor-1 (PAI-1), a prothrombotic factor that inhibits fibrinolysis; and intra-cellular adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule-1 (sVCAM-1), both of which reflect low-grade chronic inflammation of the endothelium (Ilie et al., 2008). ADMA, PAI-1, sVCAM-1 and sICAM-1 concentrations are elevated in women with PCOS compared with non-PCOS controls (Carmassi et al., 2005; Diamanti-Kandarakis et al., 2006a,b; Charitidou et al., 2008; Heutling et al., 2008; Ozgurtas et al., 2008; Moran et al., 2009a, 2011; Rajendran et al., 2009; Mohamadin et al., 2010) and have been shown to predict the development of CVD (Thøgersen et al., 1998; Blækenberg et al., 2001; Valkonen et al., 2001).

Lifestyle modification incorporating diet and exercise is considered the first-line treatment for the management of PCOS and its associated complications (Moran et al., 2006, 2009b; Wild et al., 2010). However, despite the well-established benefits of weight loss via moderate energy restriction and exercise on insulin resistance, hyperandrogenism and CVD risk markers in overweight women with PCOS (Andersen et al., 1995; Holte et al., 1995; Moran et al., 2003; Palomba et al., 2007; Vigorito et al., 2007; Gallauria et al., 2008; Thomson et al., 2008), there are limited data available on the effect of diet and exercise on endothelial function in women with PCOS. To date only one small (n = 9) pilot study showed reductions in PAI-1 following 4 weeks of a very low-calorie diet or 20 weeks of a low-calorie diet (Andersen et al., 1995). Previous studies have also shown a favourable effect of exercise training on endothelial function in both healthy and diseased populations, some specifically with reductions in sICAM-1 (Adamopoulos et al., 2001; Zoppini et al., 2006; Saetre et al., 2011) and sVCAM-1 (Adamopoulos et al., 2001; Rankovic et al., 2009), ADMA (Richter et al., 2005; Schlager et al., 2011; Tsarouhas et al., 2011) and PAI-1 (Jahangard et al., 2009). However, this is not a consistent effect (Olson et al., 2007) and there is limited research comparing the effects of diet with and without exercise. Previous research has also shown that combined aerobic-resistance exercise is more efficacious than aerobic or resistance training alone for improving insulin sensitivity and reducing abdominal fat in a range of obese populations (Cuff et al., 2003; Park et al., 2003). It is believed that these improvements may also translate to improvements in endothelial function due to the relationship between endothelial dysfunction and insulin resistance (Paradisi et al., 2001; Tarkun et al., 2004; Kravariti et al., 2005; Diamanti-Kandarakis et al., 2006a,b; Heutling et al., 2008; Moran et al., 2009a, 2011).

Therefore, the aims of this study were: (i) determine the additive effect of aerobic or aerobic-resistance exercise training when combined with energy restriction, in overweight women with PCOS, for improving endothelial function assessed by the measurement of ADMA, PAI-1, sVCAM-1 and sICAM-1 and (ii) determine relationships between the markers of endothelial function, hormonal profile and insulin resistance.

### Materials and Methods

#### Study design

The data analysed for this study were obtained from a subset of women who completed a large randomized controlled trial that concurrently investigated the effects of a hypocaloric diet with and without exercise training on body composition, metabolic and reproductive outcomes in overweight and obese women that has been previously reported (Thomson et al., 2008). The subset of women in this study had a sufficient volume of frozen serum sample required for the present analysis.

In brief, 104 sedentary, overweight or obese women with PCOS were recruited by public advertisement and from general practitioner and specialist clinics between April 2006 and February 2007. PCOS was diagnosed according to the Rotterdam criteria (The Rotterdam ESHRE/ASRM sponsored PCOS consensus workshop group, 2004). Potential participants were excluded if they were using fertility treatments or oral contraceptives, were smokers, pregnant, breastfeeding or had a history of cardiovascular, liver, kidney or respiratory disease, diabetes, uncontrolled hypertension (>140/90 mmHg) or cancer. Women were also excluded if they had any reproductive disorders unrelated to PCOS, thyroid abnormalities (hypothyroidism and hyperthyroidism) or non-classic adrenal hyperplasia. All experimental procedures were approved by Human Ethics Committees of the Commonwealth Scientific and Industrial Research Organization and the University of South Australia and participants provided written informed consent.

Prior to the commencement of the study, women were randomly assigned by the trial manager using computer generation to one of three 20-week lifestyle interventions: diet only (DO, ~6000 kJ/day energy-restricted high-protein meal plan (30% energy as protein, 40% as carbohydrate and 30% as fat), diet and aerobic exercise (DA, the above diet and five walking sessions/week) and diet and combined aerobic-resistance exercise (DC, the above diet and three walking and two strength training sessions/week). Participants and study staff were not blinded to the treatment allocation. Participants attended fortnightly diet counselling sessions to review dietary compliance using daily checklists of specific food quantities, and to discuss dietary issues. The exercise intensity for the aerobic and resistance training programmes were prescribed using training zones based on a percentage of the maximum heart rate (HRmax) and 1 repetition maximum (1RM), respectively, achieved during baseline exercise tests. The aerobic exercise intensity progressed from 25 to 30 min at 60–65% HRmax to 45 min at 75–80% HRmax. The resistance training programme consisted of five resistance exercises: bench press, lat pull down, leg press, knee extension and sit-ups. The training load started at 50–60% 1RM for 2 weeks, increased to 65–75% 1RM for the following weeks and was then progressively increased throughout the study. Participants attended weekly supervised exercise sessions and completed weekly exercise diaries to monitor their training progress and calculate the compliance. Compliance was calculated as the number of sessions correctly completed divided by the number of scheduled training sessions for the duration of the study.
An aerobic session was considered compliant if the participant completed the required time and intensity (measured by the average heart rate of the session) and the resistance sessions were considered compliant if the participant completed all exercises.

At baseline and after the 20-week intervention period, participants attended the CSIRO Clinical Research Unit in Adelaide, Australia after an overnight fast and had height (baseline only) and weight measured using a stadiometer (SECA, Hamburg, Germany) and electronic digital scales (Mercury, AMZ 14, Tokyo, Japan), respectively, prior to a blood sample being drawn. The total body fat mass was determined by dual-energy X-ray absorptiometry (Lunar Prodigy; Lunar Radiation Corp., Madison, WI, USA) and the abdominal fat mass was measured as previously described (Carey et al., 1996).

Fasting serum samples were collected and stored at −80°C until subsequent analysis. sVCAM-1, sICAM-1 and the total PAI-1 activity were analysed in duplicate on a Lumixin 200 Multiplex Analyser (Luminex Corporation, USA) using commercially available Milliplex MAP kits (Linco Research, St. Charles, MO, USA). The intra-assay coefficient of variations (CVs) for sVCAM-1, sICAM-1 and PAI-1 are 4.5, 7.9 and 11.8% and the inter-assay CVs are 8.5, 9.7 and 12.5%, respectively. ADMA was measured in duplicate by an enzyme immunoassay using a commercially available kit (DLD Diagnostika GmbH, Germany). The fasting insulin, homeostatic model assessment (HOMA2) and hormonal profile [testosterone, sex hormone-binding globulin (SHBG) and the free androgen index (FAI)] outcomes were measured as previously described (Thomson et al., 2008).

Data analysis
Prior to analysis, data were tested for normality and transformed where necessary (log sVCAM-1, ADMA, insulin, HOMA2, FAI and testosterone), or non-parametric tests were used (sICAM-1). Analyses were undertaken using PASW Statistics 18 (SPSS Inc., Chicago, IL, USA) with the significance set at $P < 0.05$. Data are presented as mean ± SE. For parametric data, parameters at baseline were compared using a one-way analysis of variance (ANOVA) and the change in variables across time and between treatments were compared between groups using ANOVA with repeated measures. Where a statistically significant main effect was found, differences between means were determined by post hoc analysis using Bonferroni adjustments for multiple comparisons. For non-parametric data, differences in groups were compared using the Kruskal–Wallis test. Correlation analysis using Pearson’s correlation coefficient and Spearman’s rank order correlation was performed to determine relationships between markers of endothelial function, the hormonal profile and insulin resistance. No power analysis was performed a priori because this was a secondary analysis in a subset of participants from a larger study (Thomson et al., 2008).

Results

Baseline assessments
Fifty women completed the 20-week intervention and had endothelial function markers measured (DO = 14, DA = 16, DC = 20; BMI: 36.5 ± 5.7 kg/m²; age: 30.3 ± 6.3 years; Fig 1). There were no differences at baseline between the three treatment groups for all measures ($P ≥ 0.2$; Table I). At baseline, sICAM-1 was positively associated with sVCAM-1 ($r = 0.57$, $P < 0.001$), PAI-1 ($r = 0.38$, $P = 0.001$), insulin ($r = 0.38$, $P = 0.007$) and HOMA2 ($r = 0.38$, $P = 0.007$). Higher ADMA levels were associated with lower hyperandrogenism (SHBG, $r = 0.38$, $P = 0.007$; testosterone, $r = −0.33$, $P = 0.02$; and FAI, $r = −0.31$, $P = 0.03$).

Intervention assessments
All three treatments resulted in significant weight loss (DO $7.9 ± 1.2%$, DA $11.0 ± 1.6%$, DC $8.8 ± 1.1%$; $P < 0.001$ for time; $P = 0.6$ for interaction). There were significant reductions in the total body and abdominal fat mass ($P < 0.001$ for time) with no difference between treatments for the abdominal fat mass ($−0.38 ± 0.04$ kg, $P = 0.07$ time $×$ treatment interaction) and only greater reductions in the total body fat mass in the DA group compared with the DO group (DO $−4.0 ± 0.7$ kg, DA $−8.1 ± 1.3$ kg, DC $−6.9 ± 1.0$ kg; $P = 0.04$ time $×$ treatment effect). The average compliance for exercise training was $77 ± 3.3$. There was a $23 ± 3.4$ and $17 ± 2.5$% improvement in aerobic fitness in the DA and DC groups, respectively and a $17 ± 4.9$% improvement in muscle strength in the DC group. sVCAM-1, sICAM-1 and PAI-1 levels were significantly reduced following weight loss ($P ≤ 0.01$ for time), with no differences between treatments ($P > 0.4$; Table II). There was also an overall non-significant decrease in ADMA ($P = 0.058$), with no differential effect between treatments ($P = 0.1$). There were also reductions in fasting insulin ($−4.6 ± 0.7$ mU/l), HOMA2 ($−0.6 ± 0.1$), testosterone...
(−0.4 ± 0.1 nmol/l) and FAI (−3.0 ± 0.6), and an increase in SHBG (7.4 ± 1.5 nmol/l) with no difference between treatments (time effect \( P < 0.001 \) for all measures, time × treatment \( P > 0.2 \)).

Reductions in sICAM-1 were related to reductions in obesity (weight loss, \( r = 0.37, P = 0.008 \); total body fat mass, \( r = 0.34, P = 0.02 \); and abdominal fat mass, \( r = 0.38, P = 0.007 \)) and changes in other endothelial function markers (sVCAM-1, \( r = 0.51 \); PAI-1, \( r = 0.40; \) \( P < 0.004 \)). However, after controlling for weight loss, only the association with sVCAM-1 remained (\( r = 0.44, P = 0.002 \)). Reductions in sCAM-1 were also related to reductions in testosterone (\( r = 0.32, P = 0.03 \)) and FAI (\( r = 0.33, P = 0.02 \)) and these remained after controlling for weight loss (testosterone \( r = 0.32, P = 0.03 \); FAI \( r = 0.30, P = 0.04 \)).

### Discussion

This study demonstrated that there was no difference in changes in endothelial function following 20 weeks of lifestyle modification between the two exercising groups, DA and DC. There was also no additional effect of exercise training on the endothelial outcomes assessed in this study when comparing DO to DA and DC. It is possible that the overriding energy restriction/weight loss effect masked any additional exercise benefit. There were also no differential treatment effects seen in the insulin resistance and hormonal outcomes which may explain the absence of any additional effect on endothelial function markers. However, exercise training has been shown to induce direct benefits to the endothelium as a result of increases in

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**Table I** Clinical, hormonal and biochemical baseline characteristics for participants who completed the study.

<table>
<thead>
<tr>
<th></th>
<th>DO (14/30)</th>
<th>DA (16/31)</th>
<th>DC (20/33)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>38.0 ± 1.9</td>
<td>36.5 ± 1.3</td>
<td>35.3 ± 1.1</td>
<td>0.41</td>
</tr>
<tr>
<td>Age (years)</td>
<td>29.9 ± 1.3</td>
<td>29.6 ± 1.6</td>
<td>31.2 ± 1.6</td>
<td>0.72</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>106.3 ± 6.5</td>
<td>101.7 ± 4.9</td>
<td>97.4 ± 4.4</td>
<td>0.48</td>
</tr>
<tr>
<td>Total body fat mass (kg)</td>
<td>47.8 ± 3.4</td>
<td>47.7 ± 2.5</td>
<td>46.8 ± 2.6</td>
<td>0.96</td>
</tr>
<tr>
<td>Abdominal fat mass (kg)</td>
<td>2.9 ± 0.2</td>
<td>2.7 ± 0.2</td>
<td>2.8 ± 0.2</td>
<td>0.69</td>
</tr>
<tr>
<td>Fasting insulin (mU/l)</td>
<td>19.1 ± 2.3</td>
<td>15.4 ± 2.2</td>
<td>13.9 ± 1.2</td>
<td>0.21</td>
</tr>
<tr>
<td>HOMA2</td>
<td>2.5 ± 0.3</td>
<td>2.0 ± 0.3</td>
<td>1.8 ± 0.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>2.6 ± 0.2</td>
<td>2.7 ± 0.2</td>
<td>2.5 ± 0.2</td>
<td>0.84</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>26.9 ± 3.4</td>
<td>33.6 ± 3.9</td>
<td>32.6 ± 2.7</td>
<td>0.35</td>
</tr>
<tr>
<td>FAI</td>
<td>12.4 ± 2.3</td>
<td>8.6 ± 1.3</td>
<td>9.6 ± 1.4</td>
<td>0.34</td>
</tr>
</tbody>
</table>

BMI, body mass index; DO, diet only; DA, diet and aerobic exercise; DC, diet and combined aerobic-resistance exercise; SE, standard error; SHBG, sex hormone-binding globulin.

Values are mean ± SE. \( n \) = number completing the intervention/number commencing the intervention.

**Table II** Levels of endothelial function markers at baseline and after 20 weeks of diet only (DO), diet and aerobic exercise (DA) or diet and combined aerobic-resistance exercise (DC).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 0</th>
<th>Week 20</th>
<th>Change</th>
<th>( P )-value (time effect)</th>
<th>( P )-value (time × treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sVCAM-1* (ng/ml)</td>
<td>DO</td>
<td>1185 ± 60.8</td>
<td>1169 ± 58.3</td>
<td>−15.7 ± 39.8</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>DA</td>
<td>1128 ± 51.6</td>
<td>1030 ± 47.6</td>
<td>−98.2 ± 42.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>DC</td>
<td>1170 ± 65.6</td>
<td>1098 ± 62.9</td>
<td>−72.2 ± 42.2</td>
<td></td>
</tr>
<tr>
<td>sICAM-1* (ng/ml)</td>
<td>DO</td>
<td>196.6 ± 14.6</td>
<td>175.6 ± 9.8</td>
<td>−21.0 ± 9.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>DA</td>
<td>163.8 ± 10.4</td>
<td>141.9 ± 10.2</td>
<td>−21.9 ± 5.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DC</td>
<td>179.1 ± 9.6</td>
<td>155.3 ± 7.9</td>
<td>−23.8 ± 5.7</td>
<td></td>
</tr>
<tr>
<td>PAI-1* (ng/ml)</td>
<td>DO</td>
<td>212.3 ± 14.7</td>
<td>182.9 ± 6.9</td>
<td>−29.4 ± 12.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>DA</td>
<td>205.3 ± 15.0</td>
<td>179.9 ± 18.1</td>
<td>−25.4 ± 9.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DC</td>
<td>190.5 ± 15.1</td>
<td>165.1 ± 12.5</td>
<td>−25.4 ± 5.6</td>
<td></td>
</tr>
<tr>
<td>ADMA (μmol/l)</td>
<td>DO</td>
<td>0.58 ± 0.05</td>
<td>0.58 ± 0.05</td>
<td>0.0 ± 0.03</td>
<td>0.058</td>
</tr>
<tr>
<td></td>
<td>DA</td>
<td>0.60 ± 0.04</td>
<td>0.61 ± 0.05</td>
<td>0.01 ± 0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DC</td>
<td>0.55 ± 0.03</td>
<td>0.49 ± 0.04</td>
<td>−0.05 ± 0.03</td>
<td></td>
</tr>
</tbody>
</table>

ADMA, asymmetric dimethylarginine; DO, diet only; DA, diet and aerobic exercise; DC, diet and combined aerobic-resistance exercise; SE, standard error; sICAM-1, intra-cellular adhesion molecule-1; sVCAM-1, vascular cell adhesion molecule-1; SE, standard error.

Values are mean ± SE. \( n \) = number completing intervention/number commencing intervention; DO \( n = 14/30 \), DA \( n = 16/31 \), DC \( n = 20/33 \).

*Significant time effect (\( P ≤ 0.002 \)).
NO bioavailability through repetitive increase of shear stress (Walther et al., 2004). Studies have previously shown that high-intensity aerobic interval training is better at improving endothelial function than either continuous moderate-intensity aerobic training or strength training, suggesting that it produces a greater shear stress which increases NO synthase (Wisloff et al., 2007; Schjerve et al., 2008). It is possible that the intensity of the exercise programme in the current study was not high enough to see an added benefit. There have been no studies that have examined the independent effect of exercise training alone without weight loss in PCOS on these outcomes and this is an area that requires further investigation.

An improvement in the markers of endothelial function was observed following the three lifestyle modification programmes, with no differences between treatments. There were reductions in sVCAM-1, sICAM-1 and PAI-1 observed at the end of the study. However, due to the lack of a non-dieting control group, it cannot be determined if these changes occurred due to the high-protein energy restricted diet and/or weight loss per se and it remains possible that improvements were due to factors unrelated to the diet. Nevertheless, the current data are comparable with previous studies conducted in other overweight and obese populations that have shown reductions in PAI-1 (Hamdy et al., 2003; Meckling et al., 2004; Murakami et al., 2007; Keogh et al., 2008), sVCAM-1 (Keogh et al., 2008) and sICAM-1 (Hamdy et al., 2003; Wegge et al., 2004; Rector et al., 2006; Keogh et al., 2008) following diet-induced weight loss with or without exercise. Several pharmacological studies in women with PCOS have also shown the beneficial effects of insulin sensitizers including metformin and rosiglitazone and oral contraceptive treatment on endothelial function (by reductions in PAI-1 and VCAM levels) after 3–12 months of treatment (Diamanti-Kandarakis et al., 2006a,b; Teede et al., 2010). Endothelial dysfunction is one of the first steps in atherogenesis and the reduction in these markers following weight loss has clinical relevance for this high CVD risk population as these markers have been shown to predict the development of CVD (Thøgersen et al., 1998; Blankenberg et al., 2001; Valkonen et al., 2001). Further research is required to confirm the clinical impact of weight loss on markers of endothelial function and explore the mechanisms behind any improvements.

Previous studies have shown a relationship between vascular dysfunction and insulin resistance (Paradisi et al., 2001; Kravariti et al., 2005; Diamanti-Kandarakis et al., 2006a,b; Heutling et al., 2008; Moran et al., 2009a, 2011), hyperandrogenism (Paradisi et al., 2001; Kravariti et al., 2005; Diamanti-Kandarakis et al., 2006a,b; Heutling et al., 2008; Ozgurtas et al., 2008; Moran et al., 2009a, 2011; Teede et al., 2010) and chronic inflammation in women with PCOS (Diamanti-Kandarakis et al., 2006a,b; Moran et al., 2009a, 2011). In support, in the present study, sICAM-1 was associated with insulin resistance (fasting insulin and HOMA2) at baseline, and reductions in sICAM-1 during the intervention were associated with reductions in the weight, total body fat and abdominal fat mass. An association between the change in sVCAM-1 and testosterone and FAI was also observed. This is similar to other reports that have shown adverse effects of testosterone/FAI on measures of endothelial function (Paradisi et al., 2001; Orlo et al., 2004; Diamanti-Kandarakis et al., 2006a,b). Testosterone has been found to promote VCAM-1 expression (McCrohon et al., 1999; Zhang et al., 2002). However, the contribution of hyperandrogenism to endothelial dysfunction remains controversial with reports that testosterone attenuates the expression of VCAM-1 in human umbilical vein endothelial cells, thus inhibiting the adhesion of monocytes to endothelial cells (Mukherjee et al., 2002), while other studies have shown no association between testosterone and endothelial function (Meyer et al., 2005). Furthermore, higher levels of ADMA were associated with lower levels of hyperandrogenism in the present study, which contrasts with previous reports (Heutling et al., 2008; Ozgurtas et al., 2008; Moran et al., 2009a). The specific reason for this discrepancy remains unclear. It has been previously demonstrated that increasing testosterone levels reduce ADMA levels; however, this occurred following testosterone administration in males in a hypogonadal state (Cakir et al., 2005; Leifke et al., 2008). Gender-related effects are thought to exist, suggesting that women with PCOS who have higher levels of testosterone may respond differently. Further research in women with PCOS is needed to understand this relationship. Irrespective of the precise mechanism, collectively the current and previous data suggest that metabolic and hormonal disturbances are associated with markers of vascular pathology in women with PCOS (Diamanti-Kandarakis et al., 2006a,b) and that weight loss induced by caloric restriction may attenuate this effect.

An important limitation of the current study is that because the original intervention (Thomson et al., 2008) was not designed to address endothelial function and the current data were obtained by analysis of stored blood samples, an a priori power analysis could not be performed. A post hoc power analysis suggests that, due to the relatively small sample size, the study may have been underpowered to detect differences between the treatment groups (power <45%, P <0.05). It is possible that exercise may have an additional benefit; however, large studies are needed to determine this. While there were no significant differences between the three treatment groups, it does appear that those in the DO group were slightly heavier and had higher levels of hyperinsulinaemia and hyperandrogenism at baseline compared with DA and DC. Thus, it is possible that this lack of difference is due to the small sample size and lack of power.

Conclusions

In summary, the addition of aerobic and combined aerobic-resistance exercise to an energy restricted diet did not provide further improvements in endothelial function in overweight and obese women with PCOS. The study was underpowered and had a small sample size. However, this study did provide an opportunity to examine the impact of lifestyle management and exercise on these outcomes in women with PCOS and will provide a direction for further investigations. This is an area of importance where there is currently a lack of data describing these effects and additional research is needed. Given that PCOS is associated with an elevated CVD risk and reduced endothelial functioning increases the CVD risk, research is needed to support the clinical importance of lifestyle modification for the management of PCOS.

Acknowledgements

We gratefully acknowledge Lisa Moran and Catherine Yandell for assistance with the measurement of the endothelial function markers. For the larger intervention, we gratefully acknowledge: Julia Weaver
for assisting with trial management; Lindy Lawson and Rosemary McArthur for their assistance in the nursing activities; Gemma Williams, Xenia Cleanthous, Siew Lim and Julianne McKeeough for their dietetic guidance and Mark Mano, Cathryn Seccafien and Candita Sullivan for laboratory assistance.

Authors’ roles
R.L.T. participated in the study design, execution, analysis, manuscript drafting and critical discussion. G.D.B. and J.D.B. participated in the study design, manuscript drafting and critical discussion. M.N., R.J.N. and P.M.C. contributed to the study design and the preparation of the manuscript.

Funding
The larger study was funded by a project grant from the National Health and Medical Research Council of Australia to investigate the long-term independent and combined effects of exercise and dietary weight loss on overweight/obese women with PCOS (#401817). Funding for the endothelial function assays was provided by a Divisional Research Development grant from the University of South Australia, Division of Health Sciences.

Conflict of interest
None declared.

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