Insulin resistance is not strictly associated with energy intake or dietary macronutrient composition in women with polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder characterized by hyperandrogenism and chronic anovulation. Around 60% of PCOS patients are obese. Weight loss has consistently been shown to improve the clinical status of women with PCOS. We hypothesized that dietary factors are associated with the hormonal and metabolic abnormalities of PCOS. This case-control study included 43 women with PCOS and 37 ovulatory, nonhirsute controls matched to the study group by body mass index. Age ranged from 14 to 38 years. Both groups underwent anthropometric, laboratory, and nutritional assessment. End points included diet composition, body fat, and hormonal and metabolic variables related to insulin resistance. The groups had similar intake of energy, carbohydrate (53.51% ± 8.36% vs 51.83% ± 10.06%), protein (15% [12-18] vs 16% [13-19]), and total fat (30.51% ± 7.90% vs 30.80% ± 7.97%). Total body fat, sum of trunk skinfold measurements, and waist circumference were higher in the PCOS group (P < .05). Sex hormone–binding globulin was lower in PCOS patients than in controls, whereas total testosterone, free androgen index, postprandial glucose, fasting and postprandial insulin, homeostatic model assessment index, triglycerides, and total and low-density lipoprotein cholesterol (P < .050) were higher. Homeostatic model assessment index was correlated with central obesity in PCOS patients and controls alike. No association was detected between androgen status and macronutrient intake. In conclusion, central obesity and insulin resistance were not strictly associated with energy intake or dietary macronutrient composition in women with PCOS.

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Keywords: Food intake; Central obesity; Insulin resistance; Nutritional sciences; Sex steroid hormones; Women

Abbreviations: BMI, body mass index; BP, blood pressure; CV, coefficients of variation; FAI, free androgen index; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; PCOS, polycystic ovary syndrome; SD, standard deviation; SHBG, sex hormone–binding globulin; TT, total testosterone.

1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder, affecting 5% to 10% of women of reproductive age. It is a major cause of anovulatory infertility, irregular menstrual cycles, and hirsutism [1-6]. Obesity is present in 30% to 75% of women with PCOS. Abdominal obesity is found in most of these women in association with metabolic disturbances [3-5,7,8], whereas insulin resistance may occur independently of body mass index (BMI), with an adverse impact on lipid profile and blood pressure (BP) [8-11]. A genetic basis has been proposed for PCOS because the prevalence of this disease is higher among family members [12,13]. However, the heterogeneous clinical presentation of...
PCOS, especially concerning the presence of central adiposity, overweight, and obesity, is indicative of a complex interaction between genetic and environmental factors [7]. In this sense, differences in dietary intake between women with PCOS and healthy controls have been described [14], as well as a tendency to overeat, particularly sweet or starchy foods [15].

In Brazil, the highest rates of obesity and overweight in women (14.4% and 42.4%, respectively) occur in the South [16]; but few data are available concerning the implications of lifestyle and dietary pattern on the prevalence of obesity and insulin resistance in PCOS [9,14,17,18]. In addition, despite the substantial evidence supporting an effect of underweight and excess weight on fertility [17], little is known about the influence of dietary quality on metabolic and endocrine control in PCOS [19]. Nevertheless, weight loss has consistently been shown to improve the clinical status of PCOS women [18,20].

Taking all these into consideration, we hypothesized that dietary intake is associated with insulin resistance, lipid profile, and hormone abnormalities in a sample of women with PCOS from the South of Brazil. To test this hypothesis, we designed a case-control study to assess dietary composition, body fat, and hormonal and metabolic variables related to insulin resistance in patients with PCOS and in a group of ovulatory, nonhirsute, BMI-matched women. Understanding the interaction between dietary factors and PCOS could provide useful insights for the management of obesity and metabolic abnormalities in affected women.

2. Methods and materials

2.1. Subjects

This case-control study was carried out with patients from the Gynecological Endocrinology Unit at Hospital de Clínicas de Porto Alegre, Brazil. Forty-three hirsute women of reproductive age presenting oligo/amenorrheic cycles (≤9 cycles per year), increased serum testosterone levels and/or free androgen index (FAI), and absence of other disorders causing hirsutism [7,21] were included in the PCOS group. Thirty-seven BMI- and race-matched non-hirsute, BMI-matched women. Understanding the interaction between dietary factors and PCOS could provide useful insights for the management of obesity and metabolic abnormalities in affected women.

2.2. Study protocol

Anthropometric measurements were performed in duplicate and included body weight, height, BMI (current weight in kilograms divided by square meters), waist circumference (measured at the midpoint between the lower rib margin and the iliac crest, perpendicularly to the long axis of the body, with the subject standing balanced on both feet, spread approximately 20 cm apart, with both arms hanging freely) [9,22,23], hip circumference (widest circumference over the buttocks) [24], and waist-to-hip ratio. Obesity was defined as BMI of at least 30 kg/m² [25]. Hirsutism was defined as a modified Ferriman-Gallwey score of 8 or higher [26-28]. Blood pressure was measured after a rest period of 10 minutes, with the subject in the supine position [29]. Hormonal and metabolic evaluation was performed between days 2 and 10 of the menstrual cycle or on any day if the patient was amenorrheic. After a 12-hour overnight fast, blood samples were drawn from an antecubital vein for determination of plasma cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides at baseline, and glucose and insulin before and 2 hours after the ingestion of a 75-g oral glucose load. Impaired glucose tolerance was determined by glucose levels between 140 and 200 mg/dL, as defined by the World Health Organization [30]. Blood samples were also drawn for measurement of sex hormone-binding globulin (SHBG) and total testosterone (TT). All samples were obtained between 8:00 AM and 10:00 AM. Free androgen index was estimated by dividing TT (in nanomoles per liter) by SHBG (in nanomoles per liter) and multiplying by 100. Homeostasis model assessment (HOMA) index was calculated by dividing insulin (in micro–international units per milliliter) by glucose (in millimoles per liter) and dividing this product by 22.5 [31]. The cutoff point to define insulin resistance was arbitrarily defined as a HOMA index of at least 3.8 [23].

2.3. Biochemical and hormonal assays

Total cholesterol, HDL-cholesterol, triglycerides, and glucose were determined by colorimetric-enzymatic methods using the Bayer 1650 Advia System (Mannheim, Germany). Non–HDL-cholesterol levels were calculated by subtracting HDL-cholesterol from total cholesterol values. Low-density lipoprotein (LDL) cholesterol was estimated indirectly using the following formula: LDL = total cholesterol – HDL – triglycerides/5. Hormonal measurements were performed using commercially available kits, as previously described [23,32,33]. Serum luteinizing hormone (LH) was measured by a specific immunometric assay (Diagnostic Products Corporation–DPC, Los Angeles, CA) with sensitivity of 0.05 mIU/mL and intra- and interassay coefficients of variation (CVs) of 3.6% and 6.7%, respectively. Total testosterone levels were measured by radioimmunoassay (ICN, Costa Mesa, CA) with an intra- and interassay CVs of 10% and 11.6%, respectively. Sex hormone–binding globulin was measured by chemiluminescent enzyme immunoassay (DPC) with a sensitivity of 0.2 nmol/L and intra- and interassay CVs of 6.1% and 8.0%, respectively. Serum insulin levels were measured with an electrochemiluminescence immunoassay (Roche
Diagnostik GmbH, D-68298 Mannheim, Germany) with a sensitivity of 0.20 mIU/mL and intra- and interassay CVs of 1.8% and 2.5%, respectively.

2.4. Measurement of skinfold thicknesses

Skinfold thickness was estimated using a caliper (Cescorf, Mitutoyo, Porto Alegre, Brazil) with 0.1-mm scale and a jaw pressure of 10 g/mm^2. Measurements were obtained at the triceps and subescapular, abdominal, and suprailiac regions. Percentage body fat was calculated using the Faulkner (1968) formula: percentage total body fat = (triceps + subescapular + suprailiac + abdominal skinfolds × 0.153) + 5.783. The sum of 3 skinfold measurements (subescapular, suprailiac, and abdominal, referred to as the sum of trunk skinfolds and expressed in millimeters) was used to estimate truncal adiposity, as previously reported [23].

2.5. Nutritional assessment

To determine the amount and quality of all foods and beverages consumed the day before, a validated 24-hour dietary recall based on individual interviews was used [34-36]. Each participant answered the questionnaire specifying details about the brand, size, and volume of each portion consumed based on food replicas, drawings and photographs, and home utensils (such as glasses, cups, mugs, and spoons) displayed during the interview. To estimate macronutrient intake and the reliability of our 24-hour dietary recall interviews, urea and creatinine were determined in 24-hour urine samples. Agreement was assessed by estimating protein intake according to the dietary recall and comparing this estimate to urea and creatinine measurements [37]. Protein balance was determined on the basis of 24-hour urinary urea using the following formula: protein intake (grams of protein per day) = nitrogen intake × 6.25, where nitrogen intake = urinary urea nitrogen (urinary urea/2) + nonurea nitrogen (losses through skin, hair, nails, and others = 0.031 g/kg current weight). This calculation took into account the excretion in the urine of most of the amino acid–derived nitrogen produced by protein catabolism [38].

2.6. Statistical analyses

Results are presented as means ± standard deviation (SD), except in the case of nonparametric data, which are presented as medians and interquartile range. Two-tailed Student t tests were used to compare the differences between means of parametric continuous variables. The Mann-Whitney U test was used for comparisons of nonparametric data. Statistical significance for categorical variables was calculated by Pearson χ² test. Spearman rank correlation coefficient was calculated between variables using a 2-tailed significance test for variables with non-Gaussian distribution. Sample size calculation was based on a previous clinical trial (Clinical Trial Registration Number: NCT01184963) carried out by our group. In that project, the primary outcome was weight loss in PCOS patients and controls following specific diets. In all cases, statistical analysis was performed using the Statistical Package for the Social Sciences 16 (SPSS Inc, Chicago, IL). Data were considered to be significant at P < .05.

3. Results

Twenty-eight (90%) of 31 PCOS patients and 26 (74%) of 35 controls were white. The remaining participants were of mixed African and European descent. Mean age in the PCOS group was 22.67 ± 5.55 years vs 29.70 ± 4.93 years for controls (P = .001). Participants in both groups were predominantly obese (57% and 50% for PCOS and controls, respectively), whereas 25% and 31% of participants in the PCOS and control groups were overweight, respectively. Normal weight was observed in 18% and 19% of participants in the PCOS and control groups, respectively.

Table 1 summarizes the clinical and anthropometric profile of each group. Body mass index was similar in both groups. The PCOS patients had higher percentage body fat (P = .007) and sum of trunk skinfolds (P = .002), and increased waist circumference (P = .029) and waist-to-hip ratio (P = .001) as compared with controls.

Table 2 shows the hormonal and metabolic profile of the PCOS and control groups. The PCOS patients had significantly lower SHBG levels and higher TT, FAI, postload glucose, fasting and postload insulin, HOMA index, triglycerides, total cholesterol, and LDL-cholesterol compared with control women. No between-group differences in fasting glucose or HDL-cholesterol were observed. Twenty-two (53%) of 43 PCOS patients and only 2 (5.5%, P < .05) of 36 controls had insulin resistance (HOMA >3.8).

Regarding food intake (Table 3), there were no statistical differences in energy, carbohydrate, protein, and lipid intake between groups. Patients with PCOS had a slightly lower protein intake than the control group (P = .05). Macronutrient intake was in accordance with National Institutes of Health recommendations [39], although both soluble (5–10 g/d) and insoluble (15–20 g/d) fiber intakes were lower than recommended [40].

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>PCOS (n = 43)</th>
<th>Controls (n = 37)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Weight (kg)</td>
<td>79.64 ± 15.04</td>
<td>77.03 ± 13.95</td>
<td>.420</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.92 ± 5.48</td>
<td>29.66 ± 5.16</td>
<td>.290</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>121.45 ± 15.81</td>
<td>116.32 ± 9.56</td>
<td>.080</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>77.56 ± 11.7</td>
<td>74.03 ± 10.18</td>
<td>.171</td>
</tr>
<tr>
<td>Skinfold thickness total body fat (%)</td>
<td>30.71 ± 6.67</td>
<td>26.8 ± 5.85</td>
<td>.007</td>
</tr>
<tr>
<td>Sum of trunk skinfolds (mm)</td>
<td>127.92 ± 36.51</td>
<td>104.34 ± 29.95</td>
<td>.002</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>90.83 ± 11.33</td>
<td>85.48 ± 9.94</td>
<td>.029</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.82 ± 0.07</td>
<td>0.77 ± 0.05</td>
<td>.001</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD (Student t test).
Other nutrients were found to be within the reference range [39]: carbohydrate, roughly 50% to 55%; protein, 15%; and total fat, around 30% of total energy intake (Table 4). Intake of cholesterol (<300 mg/d) and saturated fatty acids (8%-10%) was also within the reference range. Intake of monounsaturated fatty acids (>15%) and of polyunsaturated fatty acids (>10%) was slightly below recommended levels [39].

Homeostasis model assessment was positively associated with BMI (r = 0.680, P = .0001 in PCOS and r = 0.645, P = .0001 in controls), percentage body fat (r = 0.709, P = .0001 in PCOS and r = 0.623, P = .0001 in controls), and sum of trunk skinfolds (r = 0.715, P = .0001 in PCOS and r = 0.635, P = .0001 in controls). These associations remained significant after adjustment for FAI. No correlations between total energy intake and androgen status were observed.

4. Discussion

Few studies so far have addressed the interaction between dietary quality and endocrine abnormalities in PCOS [41-43]. In the present study, no differences were observed between southern Brazilian women with PCOS and controls in terms of energy or macronutrient intake. This finding contradicts our initial hypothesis that dietary intake would be associated with insulin resistance, lipid profile, and hormone abnormalities in PCOS. Although the high prevalence of obese women in both groups might have resulted in a lower discriminative effect, which would preclude detection of differences, previous studies [14] have reported similar results in US PCOS patients and controls with BMI values similar to those of our subjects. In addition, a study comparing Italian and US women with PCOS found no statistical differences in energy and nutrient intake between the 2 groups, whereas saturated fat intake was almost twice as high in US as compared with Italian women [44]. However, the fact that US participants had higher BMIs than those in the Italian group may have affected this result.

Some investigators have suggested that women with PCOS have a tendency to overeat, either for emotional [45] or for biological reasons. Holte et al [46] postulated that

<table>
<thead>
<tr>
<th>Variable</th>
<th>PCOS (n = 43)</th>
<th>Controls (n = 37)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT (ng/mL)</td>
<td>1.10 (0.90-1.40)</td>
<td>0.32 (0.21-0.39)</td>
<td>.001</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>28.50 (14.80-50.60)</td>
<td>44.60 (29.55-56.04)</td>
<td>.030</td>
</tr>
<tr>
<td>Free androgen index a</td>
<td>19.90 (9.93-29.96)</td>
<td>2.76 (1.70-4.70)</td>
<td>.001</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>88.69 ± 8.92</td>
<td>88.89 ± 7.08</td>
<td>.910</td>
</tr>
<tr>
<td>Glucose 129 (mg/dL)</td>
<td>118.15 ± 28.72</td>
<td>96.43 ± 18.24</td>
<td>.001</td>
</tr>
<tr>
<td>Fasting insulin (μIU/mL)</td>
<td>17.75 (10.95-33.60)</td>
<td>10.57 (5.97-13.73)</td>
<td>.001</td>
</tr>
<tr>
<td>Insulin 129 (μIU/mL)</td>
<td>126.90 (56.45-190.60)</td>
<td>49.86 (27.70-85.48)</td>
<td>.001</td>
</tr>
<tr>
<td>HOMA index</td>
<td>3.85 (2.30-7)</td>
<td>2.13 (1.30-3.16)</td>
<td>.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>86 (60-1420)</td>
<td>63 (48.50-97.50)</td>
<td>.043</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>170 ± 47.84</td>
<td>162.91 ± 35.05</td>
<td>.019</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>51.34 ± 10.19</td>
<td>52.02 ± 12.83</td>
<td>.790</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>155.56 ± 42.92</td>
<td>136.42 ± 33.41</td>
<td>.031</td>
</tr>
</tbody>
</table>

Values represent means ± SD or median and interquartile range (25% to 75%). Statistical comparisons were performed by Student t test for means and by Mann-Whitney U test for medians.
insulin-resistant PCOS patients experience recurrent hypoglycemia. These hypoglycemic episodes could cause carbohydrate cravings and decreased postprandial satiety, leading to overeating and obesity. Other studies on disordered metabolism and PCOS have produced contradictory findings [47,48]. Robinson et al [48] found that obese and lean women with PCOS exhibited reduced postprandial thermogenesis (a measure of metabolic efficiency) compared with obese and lean women without PCOS; the reduction in postprandial thermogenesis in women with PCOS was correlated with reduced insulin sensitivity. In contrast, other studies [49] found no difference in resting metabolic rate or postprandial thermogenesis between obese women with and without PCOS.

The present study shows that, despite being younger than controls, participants with PCOS had more central obesity as measured by the sum of trunk skinfolds, waist circumference, and waist-to-hip ratio. Central obesity, defined as increased abdominal fat, is a marker of insulin resistance and a risk factor for cardiovascular disease [50,51]. In fact, PCOS patients have been considered a high-risk subgroup for diabetes and cardiovascular disease. In our study, women with PCOS also had lower SHBG and higher androgen levels and a more adverse metabolic profile than the control group. This suggests that insulin resistance leads to both an increase in ovarian androgen secretion and a reduction in SHBG levels. Hence, obese women with PCOS are frequently more hyperandrogenic that nonobese ones [54-57].

A complex interrelationship between different nutritional factors and endocrine status is recognized. The quality of diet seems to play a role in the regulation of sex steroid metabolism. In this sense, it is reasonable to presume that a low-fiber, high-lipid diet may increase circulating estrogen and androgen concentrations [58], whereas a very lipid-rich diet may decrease SHBG concentrations, with a consequent increase in both androgen and estrogen availability to target tissues [41]. In the present study, HOMA index was correlated with markers of central obesity such as waist circumference and sum of trunk skinfolds in both the PCOS and control groups; but no associations were found between androgen status and macronutrient intake.

One limitation of the present study is the high prevalence of overweight and obesity among both PCOS and control groups. This precludes extrapolation of our findings to populations of lean women with PCOS (BMI <25), although insulin resistance and central adiposity are also frequent in those women compared with healthy women with the same BMI.

In conclusion, PCOS patients did not differ from controls in terms of the amount and quality of dietary macronutrient intake. Women with PCOS, however, had greater waist circumference and HOMA index, as well as a more adverse lipid profile, than the control group. This suggests that insulin resistance is not strictly associated with energy intake or dietary composition in PCOS.

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