Metabolic syndrome in young Czech women with polycystic ovary syndrome

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METHODS: Sixty-nine young women with polycystic ovary syndrome (PCOS) [age 25.2 ± 4.7 years, with body mass index (BMI) 24.3 ± 4.8 kg/m²; mean ± SD] and 73 age-matched healthy females (BMI 22.3 ± 3.3 kg/m²; mean ± SD) were evaluated for the occurrence of features of metabolic syndrome according to the Adult Treatment Panel III.

RESULTS: Overt metabolic syndrome (the presence of three and more risk factors) was not more common in PCOS women (1/64, 1.6%) than in healthy controls (0/73, 0%). On the other hand, in nearly 50% of PCOS women isolated features of metabolic syndrome, most often a decrease in high-density lipoprotein (HDL) cholesterol, were found. Women with at least one feature of metabolic syndrome were, in comparison with women without any of these features, significantly more obese (P = 0.0001), with lower insulin sensitivity (P = 0.05). When comparing PCOS women according to the degree of insulin sensitivity, as determined by euglycaemic clamp, isolated features of metabolic syndrome were found in 8/17 women above the upper quartile, compared with 11/16 women below the lower quartile of insulin sensitivity (P = 0.20). CONCLUSIONS: Overt metabolic syndrome is only rarely encountered in young Czech females affected by PCOS but its isolated features are relatively frequent, both in young PCOS patients and in age-matched control women.

Key words: euglycaemic clamp/insulin resistance/metabolic syndrome/polycystic ovary

Introduction

Polycystic ovary syndrome (PCOS) seems to be the most common endocrine disease in women of reproductive age, with the incidence reported to be about 4–6% in this age group for white women (Knochenhauer et al., 1998; Azziz et al., 2004). In the last two decades of the 20th century, insulin resistance (Dunaif et al., 1989; Diamanti-Kandarakis et al., 1995; Toprak et al., 2001), dyslipidaemia (Wild et al., 1985; Talbott et al., 1998; Legro et al., 1999, 2001; Dejager et al., 2001; Pirwany et al., 2001) and obesity (Ehrmann et al., 1999; Legro et al., 1999) began commonly to be described as associated with PCOS. These disorders are also the features of the so-called metabolic syndrome or syndrome X, as defined by either the World Health Organization or the Adult Treatment Panel (ATP III) (2001). Insulin resistance is thought to be a core defect in metabolic syndrome, but assessments of neither insulin resistance nor hyperinsulinaemia are among the diagnostic criteria for the syndrome proposed by The National Cholesterol Education Program (NCEP)/ATP III (2001). The exact relationship between insulin resistance and different features of syndrome X is unknown. There is also some discussion as to whether PCOS itself could be another feature of syndrome X (Sam and Dunaif, 2003).

On the other hand, a surprisingly low number of women with metabolic syndrome have been shown to be affected by PCOS (Korhonen et al., 2001). To date there are few data concerning the prevalence of metabolic syndrome in PCOS women, and these data are mainly derived from the US population (Glueck et al., 2003; Apridonidze et al., 2005), where significantly more women are obese in comparison with European studies.

The authors evaluated a group of young women with PCOS in comparison with age-matched healthy women for the occurrence of various features of metabolic syndrome according to ATP III. A second aim was to describe the mutual relationship of different features of metabolic syndrome to insulin resistance, as examined by euglycaemic hyperinsulinaemic clamp.

Materials and methods

Patients

The study group comprised 69 oligo/amenorrhoeic women with PCOS, evaluated in the years 2001–2003 at either the Department of
Clinical Endocrinology of the Institute of Endocrinology, Prague, Czech Republic or at the endocrine outpatient clinic of the Department of Obstetrics and Gynaecology, Charles University, Prague, and willing to undergo a euglycaemic clamp. All of the subjects matched the Rotterdam consensus criteria (2004), and all had a clinical manifestation of hyperandrogenaemia as hirsutism and/or acne, and an elevation of the free testosterone index and/or androstenedione above the upper limit of the normal range, i.e. 0.40–2.65 nmol/l for testosterone and 1.6–5.4 nmol/l for androstenedione (Vrbikova et al., 2004). Pelvic ultrasound was done using the Siemens Sienna system, (Siemens Medical Solutions, Ultrasound Division, Mountain View, CA, USA), with a 5/7.5 MHz vaginal ultrasound probe. The women were otherwise in good health, without any serious disorders. Women suffering from epilepsy or migraines were excluded, as these are contraindications for the euglycaemic clamp. In all patients 17-OH progesterone was determined in the early follicular phase of their cycle, and if levels were between 5 and 10 nmol/l an adrenocorticotrophic hormone test was performed to exclude late-onset congenital adrenal hyperplasia. Hyperprolactinaemia (prolactin level >20 μg/l), hypercortisolism (plasma cortisol >650 nmol/l and, if necessary, urinary free cortisol excretion (normal if <280 nmol/24 h) or a short dexamethasone suppression test with 1 mg of dexamethasone at 22.00–23.00 h and subsequent morning plasma cortisol (normal if <80 nmol/l)), and thyroid dysfunction (euthyroidism defined as both thyroid-stimulating hormone and free thyroxine in normal range) were excluded. None of the patients had taken oral contraceptives or any other medication affecting steroid or glucose metabolism during the preceding 3 months. The control group consisted of 73 healthy, age-matched females recruited by advertisement, all of whom were in good health with no serious disorders, with a regular menstrual cycle (21–35 days), with no clinical signs of hyperandrogenism and with serum testosterone lower than 2.65 nmol/l. Pelvic ultrasonography was not performed. The patients used no medication. The local ethics committee of the Institute of Endocrinology approved the protocol of the study and all the patients and controls signed informed consent before the examinations. The patients and controls were evaluated at the clinical department of the Institute of Endocrinology as outpatients. Two blood pressure readings were obtained in sitting patients after a 10-min rest; the mean was determined from two values and was used for further analysis. Waist circumference was measured in the standing position, halfway between the lower ribs and the crest of the pelvis. Blood sampling for hormonal and biochemical examination was done between days 3 and 6 of the menstrual cycle or, in the case of secondary amenorrhoea, at any time. Metabolic syndrome was defined using the ATP III criteria (1997), as the presence of three or more of the following features: (i) abdominal obesity (waist circumference ≥88 cm); (ii) hypertriglyceridaemia (>1.69 mmol/l); (iii) decrease in high-density lipoprotein (HDL) cholesterol (<1.29 mmol/l); (iv) high blood pressure (≥130/85 mmHg); (v) high fasting blood glucose (≥6.1 mmol/l).

In PCOS patients, after basal blood samples were taken, a 2-h euglycaemic hyperinsulinaemic (1 mIU kg⁻¹ min⁻¹) clamp was performed as described previously (DeFronzo et al., 1979). Insulin sensitivity was determined from the values obtained during the steady-state period, between the 100th and 120th minutes. The target blood glucose level was 5.0 mmol/l, with the coefficient of variance less than 5%. The glucose disposal rate, defined as the amount of glucose supplied by the infusion to maintain the desired blood glucose level (μmol kg⁻¹ min⁻¹), and the insulin sensitivity index (ISI), defined as the ratio of the glucose disposal rate to the average insulin concentration during the observed period (ISI, μmol kg⁻¹ min⁻¹ per mlU l⁻¹ × 100), were calculated on the basis of the clamp results.

Blood glucose was determined in the whole blood by the electrochemical method (Super GL, Dr Muller Gerate Bau, GmBH, Freital Germany). Insulin was estimated by immunoradiometric assay using an immunoradiometric assay kit (Immunotech, Marseilles, France). Total cholesterol, HDL cholesterol and triglycerides were assessed by photometry (Ecoline 25; Merck Vitalab Eclipse, Darmstadt, Germany). Testosterone, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulphate, LH and sex hormone binding globulin were determined as described previously (Vrbikova et al., 2001).

Statistical evaluation
After confirming a Gaussian distribution, Student’s t-test was used to evaluate differences between the controls and the PCOS women. Results are presented as mean ± SD. The χ² test or Fisher’s exact test was used to compare the frequencies of the particular features of metabolic syndrome between PCOS women and controls.

Results

Clinical parameters

The demographic, anthropometric and biochemical parameters of the healthy and PCOS women are given in Table I. Vaginal pelvic ultrasonography was carried out in 58 PCOS patients. Six showed a normal appearance of the ovaries and 52 had polycystic ovaries (PCO) Five PCOS women had regular menstrual cycles; in 50 women oligomenorrhoea and in 14 secondary amenorrhoea was observed. Body mass index (BMI) in PCOS women was significantly higher than in the controls.

| Table I. Basic demographic and metabolic parameters in healthy women and women with polycystic ovary syndrome (PCOS) |
|---|---|---|
| **Controls (n=73)** | **PCOS (n=69)** | **P** |
| Age (years) | 23.8 (21.8; 26.8) | 24.0 (22.0; 28.0) | n.s. |
| Body mass index (kg/m²) | 21.9 (20.2; 23.6) | 23.0 (21.0; 26.9) | 0.0097 |
| Waist (cm) | 68.2 (65.4; 73.4) | 74 (68.5; 80.0) | 0.0009 |
| Systolic blood pressure (mmHg) | 110.0 (103.3; 118) | 118 (110.3; 127.5) | 0.003 |
| Diastolic blood pressure (mmHg) | 70.0 (65.0; 76.0) | 75 (70; 79) | 0.02 |
| Cholesterol (mmol/l) | 4.08 (3.75; 4.51) | 4.44 (4.08; 4.79) | 0.01 |
| Triglycerides (mmol/l) | 0.79 (0.61; 1.08) | 0.86 (0.65; 1.19) | n.s. |
| HDL cholesterol (mmol/l) | 1.48 (1.29; 1.64) | 1.37 (1.25; 1.62) | 0.04 |
| Fasting blood glucose (mmol/l) | 4.5 (4.2; 4.7) | 4.6 (4.20; 4.82) | n.s. |
| Testosterone (nmol/l) | 1.83 (1.55; 2.35) | 3.38 (2.42; 4.27) | 0.00001 |
| Fasting insulin (mIU/l) | 6.30 (4.80; 9.28) | 8.24 (5.25; 10.05) | n.s. |

Values are median (lower quartile; upper quartile). HDL cholesterol, high-density lipoprotein cholesterol.
(24.3 ± 4.8 versus 22.3 ± 3.3 kg/m², P = 0.001) and all other variables were adjusted for BMI. After BMI adjustment, significantly higher waist circumference (P = 0.0009), systolic blood pressure (P = 0.003), diastolic blood pressure (P = 0.02) and cholesterol (P = 0.01) and significantly lower HDL cholesterol (P = 0.04) were found in the PCOS women than in controls.

The occurrence of the individual features of metabolic syndrome (according to NCEP/ATP III) in PCOS and controls is given in Table II. No significant difference in the occurrence of any of the features of metabolic syndrome was found between Czech PCOS women and the controls. In PCOS women the following combinations were found: reduction of HDL cholesterol with an increase in waist circumference (two patients), and reduction in HDL cholesterol with elevation of triglycerides (two patients). Other possible combinations were not encountered. Overt metabolic syndrome (higher blood pressure with higher triglycerides and lower HDL cholesterol) was found in only one patient.

To evaluate whether the occurrence of the individual features of metabolic syndrome are different in insulin-sensitive and insulin-resistant PCOS, women were compared on the basis of the degree of insulin sensitivity. Initially, 17 women with ISI below the lower quartile of insulin sensitivity (44.8 ± mol kg⁻¹ min⁻¹ per mIU L⁻¹ × 100) were compared with the remaining 52 women. The occurrence of low HDL cholesterol was not significantly different between the groups (33.3 versus 39%), as was also true of abdominal obesity (7 versus 10%), while arterial hypertension occurred in three women in the lower quartile versus one in the rest. When comparing women above the upper and below the lower quartiles of ISI (ISI > 80.8 versus <44.8 ± mol kg⁻¹ min⁻¹ per mIU L⁻¹ × 100), isolated features of metabolic syndrome were found in 8/17 women above the upper quartile as opposed to 11/16 women below the lower quartile (P = 0.20; χ² = 1.59.). Women with at least one feature of metabolic syndrome (n = 37) were, in comparison with women free of any of these features (n = 32), significantly more obese (BMI 26.0 ± 5.5 versus 22.3 ± 2.4 kg/m²; P = 0.0001), with lower insulin sensitivity (52.7 ± 28.5 versus 69.6 ± 25.0 μmol kg⁻¹ min⁻¹ per mIU L⁻¹ × 100; P = 0.05) and lower testosterone (3.1 ± 1.1 versus 3.8 ± 1.3 mmol/l; P = 0.03).

### Discussion

In this study, isolated features of metabolic syndrome were no more frequent in young Czech PCOS women than they were in healthy females. The most common abnormality in both groups was a decrease in HDL cholesterol to below 1.3 mmol/l.

In this study, isolated features of metabolic syndrome were much less frequent in young Czech PCOS women than they were in the US population. Czech PCOS data were compared with recently published data from the USA (Apridonidze et al., 2005); it was found that all of the features of metabolic syndrome (with the exception of elevated fasting blood glucose) were significantly more common in the US population than in Czech females.

There is a paucity of data concerning the occurrence of metabolic syndrome in PCOS. A study on the occurrence of metabolic syndrome in women in the USA with PCOS was undertaken in 2003 (Glueck et al., 2003), in which all of the features of metabolic syndrome were found significantly more often in these PCOS women than in the NHANES III white female population; metabolic syndrome was diagnosed in 46% of PCOS women. Recently, a similar study in the US population has confirmed these data; the authors described a prevalence of metabolic syndrome in PCOS women twice as high as that in the general population data (Apridonidze et al., 2005). These results are different from those of the present study; the US population was slightly older (average age 31 versus 24 years), but this is probably of no great importance. Secondly, and more importantly, the US women were significantly more obese (85% with a waist circumference of over 88 cm or BMI between 31.7 and 42 kg/m²).

Higher BMI, waist circumference and systolic and diastolic blood pressures in PCOS women than in controls have already been described; thus, these results accord with those of other studies (Conway et al., 1992; Talbott et al., 1995, 1998.). On the other hand, no elevation of any of these parameters above the upper limit of the normal range (Author: as meant?) was found in PCOS women compared with their healthy counterparts. It may thus be speculated that these ‘subclinical’ risks worsen over time; contrary to this speculation, there are, however, data finding an equal metabolic risk profile between PCOS and healthy women above 40 years (Talbott et al., 1998). An alternative explanation might be that only some PCOS women are susceptible to metabolic syndrome and cardiovascular disease. The most significant difference between PCOS women with and without some features of metabolic syndrome was in the degree of obesity, compared with slight differences in insulin sensitivity. Obesity might thus be considered the most important factor aggravating cardiovascular risks in PCOS women, just as it is in the general population (St-Onge et al., 2004). This speculation is also substantiated by the comparison of data derived from Czech and US women affected with PCOS. Recent studies on metabolic syndrome derived from US data have comprised mostly women with a

<table>
<thead>
<tr>
<th>Features of metabolic syndrome</th>
<th>Prevalence: n (%)</th>
<th>P</th>
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<tbody>
<tr>
<td>Blood pressure &gt;130/85 mmHg</td>
<td>5 (6.85)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>HDL cholesterol &lt;1.29 mmol/l</td>
<td>18 (24.6)</td>
<td>24 (34.8)</td>
</tr>
<tr>
<td>Waist circumference &gt;88 cm</td>
<td>4 (5.5)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Triglycerides &gt;1.69 mmol/l</td>
<td>1 (1.4)</td>
<td>4 (5.8)</td>
</tr>
<tr>
<td>Fasting blood glucose &gt;6.1 mmol/l</td>
<td>1 (1.4)</td>
<td>0</td>
</tr>
</tbody>
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significant degree of obesity, nearly all of whom have at least one feature of metabolic syndrome, and of whom some 40–50% suffered from overt syndrome. By contrast, Czech PCOS women were mostly lean or only slightly overweight.

In individuals participating in the third national health and nutrition examination survey, (NHANES III), the odds of having metabolic syndrome increase with increasing BMI even in the high-normal range (St-Onge et al., 2004). How this translates to end-point cardiovascular events remains to be verified by long-term prospective studies. In terms of the conversion rate from normal glucose tolerance to diabetes, initial obesity (but not a moderate weight gain during the period of a 4- to 7-year follow-up) was a significant determinant of conversion (Wang and Norman, 2004).

There are some drawbacks to the present study. The control group was defined on the basis of self-reported regular menstrual cyclicity, in connection with normal plasma testosterone and no clinical signs of hyperandrogenism, such as hirsutism, acne or alopecia. Two of the three criteria of the Rotterdam consensus were therefore excluded, but ovarian morphology was not examined. A prevalence of as high as 20% PCO is detected among healthy females (Clayton et al., 1992). On the other hand, females with PCO have been reported as having higher serum testosterone than those with normal ovarian morphology (Adams et al., 2005). The authors detected no bimodal testosterone distribution, and do not therefore believe that there is a substantial proportion of unrecognised PCOS in the control group. The second drawback lies in the fact that the healthy controls were not taken from a random population sample, but rather were recruited by advertisement. Selection bias could therefore affect the results, and it is difficult to judge whether ‘healthier’ women are more likely to respond to such an advertisement, or if the opposite is true.

In conclusion, overt metabolic syndrome as defined by NCEP/ATP III is only rarely encountered in young Czech females affected by PCOS. The occurrence of the different features of this syndrome in PCOS is no more frequent than in healthy controls, despite the fact that PCOS women have higher average BMI, waist circumference and systolic and diastolic blood pressures than controls. The most commonly encountered abnormality is decreased HDL cholesterol.

Acknowledgements

This study was supported by grant 301/04/1085 of the Grant Agency of the Czech Republic and NB 7391-3 of the Czech Ministry of Health. The authors are grateful for the excellent technical assistance of Mrs R. Bajtlová and Mrs J. Novotná.

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Submitted May 14, 2005; resubmitted June 17, 2005; accepted June 29, 2005