Metabolic Syndrome in Mediterranean women with polycystic ovary syndrome: when and how to predict its onset

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Short title: Predictors of metabolic syndrome in PCOS

Key words: Metabolic syndrome; Polycystic ovary syndrome; Cardiovascular risk

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Disclosure Statement: The authors have no conflict of interest to declare.

Abstract

Polycystic ovary syndrome (PCOS) is associated with the metabolic syndrome (MetS). The metabolic disorders are not universal and may vary with race, age and phenotype. Our purpose was to determine the clinical and biochemical characteristics of Mediterranean PCOS women with MetS, compare them with non-MetS PCOS patients, and assess the ability of clinical data and biochemical tests to predict these abnormalities within our population. A total of 218 subjects, 196 PCOS women and 22 controls, undergo a physical examination and laboratory evaluation for a diagnosis of MetS. MetS was categorized according to NCEP ATP III guidelines. PCOS patients were analyzed separately and compared in three subgroups: three or more MetS criteria, two criteria, one or no criteria. The overall prevalence of MetS was 21.4%. Women with MetS had higher glucose (G) levels than PCOS women with two criteria (5.7±1.5vs 5±0.4, $p<0.05$). Both groups were comparable for all the other parameters. Waist circumference (WC), body mass index (BMI), systolic (SBP) and diastolic blood pressure (DBP), bioavailable testosterone (uT), triglycerides (TG) and insulin (I) levels were significantly higher and sex hormone-binding globulin (SHBG) levels, high-density lipoprotein (HDL), HOMA and QUICKI indexes significantly lower in both groups, MetS and patients with two criteria, compared with women with one or no criteria and the control group. WC, HDL and TG were the best predictors of PCOS patients at risk for MetS. In conclusion, we recommend considering PCOS patients with two criteria of MetS as having the same risk as patients with the full syndrome. Waist circumference with HDL and triglycerides is an efficient combined test to identify PCOS women at risk for metabolic and cardiovascular diseases.

Introduction

PCOS is a heterogeneous disorder of unknown origin characterized by hyperandrogenism, chronic anovulation and insulin resistance (IR) (1). IR, present in a significant proportion of obese women (2)(3), is recognized as a major risk factor for the development of a cluster of risk factors known as the metabolic syndrome (MetS)(4). MetS was present in 35-45% of adult women with PCOS in North American studies (5-9). However, previous reports showed the prevalence of MetS to be lower in Mediterranean countries, with these variations being attributed to differences in race, diet and lifestyle (10)(11).

Thus, PCOS is regarded as a risk factor for the development of cardiovascular disease, and general screening of PCOS patients for MetS has been recommended (12). However, there is no consensus as to who should be screened and how it should be done (8)(13)(14). However using only waist circumference implies screening a large number of subjects which in our population could be over 75% of PCOS patients. Furthermore, no prospective studies exist which analyzed the predictive power of these parameters in the general population of women with PCOS. In MetS, DM or cardiovascular disease are the consequence of an evolutive process after an associated period of IR or, in the majority of cases, of upper obesity (15)(16). Thus, the earlier these cases are identified, the sooner effective preventive measures can be implemented to prevent this evolutive process in advanced ages.

To assess MetS and IR prevalence in a Mediterranean PCOS population 218 subjects were prospectively studied in our centre

Subjects and methods

Subjects

One hundred and ninety-six women with PCOS referred to the Reproductive Endocrinology Unit of the Hospital de la Santa Creu i Sant Pau, Barcelona between 2004 and 2009 for menstrual disorders and hyperandrogenism were evaluated.

PCOS diagnosis was based on the presence of hirsutism and/or hyperandrogenism and menstrual disorders, after Cushing's syndrome, late-onset 21-hydroxylase deficiency, thyroid dysfunction, hyperprolactinemia or androgen-secreting tumor according to the 1990 National Institute of Child Health and Women Development, had been ruled out by appropriate tests. Clinical hyperandrogenism was defined as the presence of hirsutism (Ferriman–Galwey score ≥8) and/or acne (17). Biochemical hyperandrogenism was present if levels of one or more androgens -testosterone (T), androstenodione (Δ4) or 17-hydroxyprogesterone (17-OHP) or bioavailable testosterone (uT)- were above upper normal range in our population. Menstrual cycles shorter than 25 days and longer than 34 were considered abnormal.

MetS was defined according to NCEP ATP III guidelines (Expert Panel on the Diagnosis, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001)(18). MetS was diagnosed if at least three of the following five features were present: (i) WC > 88 cm, (ii) serum triglyceride (TG) ≥1.70 mmol/l, (iii) serum high-density lipoprotein (HDL) <1.30 mmol/l or the use of lipid-lowering medication, (iv) blood pressure (BP)≥ 130/85 mm Hg or the use of anti-hypertensive medication, and (v) fasting plasma glucose (G) ≥ 6.11 mmol/l. Patients with PCOS were divided into three subgroups according to the number of MetS criteria present: 90 women with one or no criteria, 64 with two and 42 with three or more.

Twenty-one women with normal BMI , regular menses and absence of clinical or biochemical hyperandrogenism and who attended for an annual examination in our Unit over the same period as the patients with PCOS served as controls.

Study Protocol

BMI and waist-to-hip ratio (WHR) were calculated. Body weight and height were measured in light clothing without shoes and BMI was calculated. Waist circumference was measured as stablished. BP was measured using a portable lightweight device.

Blood samples were drawn between the 2nd and 5th days of the menstrual cycle, if present. Hormonal and biochemical analyses included measurement of FSH, LH, T, SHBG, uT,

dehydroepiandrosterone sulfate (DHEAS), 17-OHP, Δ4), fasting insulin (I), G levels, total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), very-low-density liproprotein (VLDL) and triglycerides (TG), lipoprotein (a) (Lp(a)), apoprotein A (apo A), apoprotein B (apo B), C-reactive protein (CRP) and homocysteine.

In order to study insulin sensitivity in basal conditions, G:I ratio, QUICKI and HOMA were calculated as previously proposed (19-21).

Data were recorded and stored in a computerized database (Microsoft Office Excel 2003).

Data assays

Blood samples for hormone and routine laboratory analyses were drawn between 0800h and 0900h after a 10-12h overnight fast following the preanalytical conditions recommended. Serum or EDTA plasma was immediately separated by centrifugation and assayed fresh or frozen at –20º C until assayed. Assays were performed in serum aliquots from the following specimens: FSH, LH and T (Elecsys Modular analytics E170, Roche Diagnostics GmbH, Mannheim, Germany), prolactin, DHEAS, SHBG, Δ4, I (Immulite 2000, EURO/DPC Ltd, Llanberis, UK) and 17-OHP (Active 17α OH Progesterone RIA, DSL-5000, Diagnostic Systems Laboratories,

Inc, Webster, Texas, USA). The uT is the quotient of serum total T divided by serum SHBG × 100 [(T/SHBG) × 100]1 and results in a unitless number when both values are expressed in molar concentrations. Standard automated methods were used for hematologic analysis (Coulter Analyzer, Coulter Diagnostics, Miami FL, USA) and routine chemistries (Hitachi 747

Analyzer, F Hoffmann-La Roche Ltd, Basel, Switzerland).

TC and TG were measured by enzymatic methods and HDL by a direct method using polyethylene-glycol pretreated enzymes. All three assays were carried out in a Hitachi 911 analyzer with methods from Roche Diagnostics, Basel, Switzerland. LDL was calculated by Friedewald's formula when TG did not exceed 3.45 mmol/L; VLDL was calculated by dividing total TG (in mmol/L) by 2.17. When TG were ≥3.45 mmol/L, LDL was measured by a modified

ultracentrifugation-based (betaquantification) method with previous separation and measurement of VLDL (d<1,006 Kg/L) particles and measurement of the cholesterol in the remaining LDL+HDL fraction. ApoB and Apo A were measured by immunoturbidimetric methods (Tina-quant, Roche Diagnostics) calibrated against the WHO/IFCC reference standards SP3-07 (apo B) and SP1-01 (apo A), respectively.

LDL size was determined by electrophoresis on a polyacrylamide gel gradient (2-16%). Phenotypes A and B were defined as a predominant LDL subclass pattern with diameters of >25.5 and <25.5 nm, respectively. Lp(a) was determined using a commercial immunoturbidimetric method (Roche Diagnostics). Total homocysteine concentrations were determined using an automated fluorescence polarization immunoassay (Abbott Diagnostics, Chicago, Ill). CRP was measured with a high-sensitivity, particle-enhanced immunoturbidimetric assay (Tina-Quant ultrasensitive PCR latex, Roche Diagnostics) with a measurement range of 0.1 to 20 mg/L.

Statistics

Statistical analyses were performed with SPSS software (version 10.0; SPSS Inc., Chicago, IL, USA). Mean values are reported as ±S.E.M. unless otherwise stated. The significance of differences between groups was determined by an unpaired *t*-test for independent variables, analysis of variance (ANOVA) or the Mann-Whitney *U* test. Normal distribution was tested by the Kolmogorov–Smirnov test. Correlation coefficients among different variables were obtained using Pearson's and Spearman's methods. Differences and correlations were considered statistically significant at $P < 0.05$. Differences in frequencies were tested by the chi-square test.

Multiple regression analysis was performed to determine the prediction variables. The area under the receiver operating characteristics (ROC) curve (AUC) was used to define variables differentiating between PCOS patients with MetS or with two risk factors and patients or controls without risk. The 95% confidence interval (95% CI) for the ROC AUC was used to test

the hypothesis that the theoretical area is 0.5. If the CI did not include the 0.5 value, the laboratory test was considered to have the ability to distinguish between groups.
The crude concordance rate among different measurements of IR was also evaluated, and the Kappa score for each pair was calculated.

Results

Ninety-two women with PCOS (46.9%) were obese (BMI ≥ 30 kg/m2), while 52 were overweight (BMI ≥ 25 kg/m2 and ≤ 30 kg/m2)(26.5%). When the individual components of MetS were considered, 64.3% of PCOS women had an abnormal weight circumference, 43.9% low HDL, 32.9% high blood pressure, 9.27% raised triglycerides and only 7.15% elevated fasting glucose levels.
The overall prevalence of MetS was 21.4% (42/196): 32 cases met three criteria for MetS, 2 cases four criteria and 4 met all five criteria. All women with MetS had increased WC, 94.7% reduced fasting plasma HDL concentrations, 68.4% high BP and 31.57% elevated fasting plasma TG concentrations and increased G concentrations.
According to the WHO criteria, 14 of the women with MetS (33.3%) women presented impaired glucose tolerance (6 women: 3 on basal glucose and 3 at OGTT) or diabetes (8 women: 2 on basal glucose and 6 at OGTT). In contrast, only 6 women (11.1%) with 2 criteria of MetS had impaired glucose tolerance (2 cases) or diabetes (4 cases) and only 1 with one or no criteria of MetS had diabetes.

Clinical and biochemical characteristics of the subjects are summarized in Tables 1 and 2. Women with MetS only differed from those with two criteria of MetS in that they had higher G levels. Waist circumference, BMI, SBP and DBP, uT, TG and I levels were significantly higher and SHBG levels, HDL, HOMA and QUICKI significantly lower in patients with MetS and two criteria compared with women with one or no criteria and controls. None of the MetS PCOS patients had higher LH/FSH and fasting glucose than controls. The group with two criteria of

MetS had significantly higher T levels than MetS patients and the control group. MetS patients had higher levels of Apo B, homocysteine, CPR and G/I ratio and lower Apo A than PCOS patients with one or no criteria and the control group. MetS patients and controls also differed significantly in relation to LDL levels.

The relative risk and 95% confidence interval of MetS for women with WC > 88 cm was 27.8 (1.62-478.9), 21.2 (2.9-152.6) if HDL levels were <1.30 mmol/l, 6 (3.35-10.79) in PCOS women with high fasting G, 5.69 (2.05-15.79) if BP was ≥ 130/85 mm Hg and, finally, 4 (1.97-8.18) in cases of TG ≥1.70 mmol/l.

We aimed to ascertain whether these parameters could be useful predictors of metabolic status in PCOS women. Univariate logistic analysis revealed an association between PCOS patientswith MetS or with two criteria with BMI, WC, uT, SHBG, HDL, TG, homocysteine, CRP, HOMA and QUICKI. As predictive variables, either WC in combination with HDL or WC, HDL and TG were included in the final model. The AUC was 0.951 (95% CI = 0.925-0.977) for WC with HDL and TG and 0.923 (95% CI = 0.883–0.963) for WC and HDL alone (Figure 1).

Discussion

This study showed a prevalence of MetS in our population of PCOS patients much higher than the 5% reported in the general population (22). It cannot be ruled out that the high proportion of obese patients included in our study could stem from a selection bias, since our center, might accumulate cases with poor prognosis, with both obesity rates and MetS being overexpressed. Discrepancies exist as to what extent obesity constitutes a determinant factor in the rising prevalence of MetS in PCOS patients. (7)(8)(12)(23)(24). In our population, MetS is limited almost exclusively to obese patients. However, up to a quarter of women with PCOS and less than two MetS criteria were obese with similar results regarding waist circumference: > 88 cm. These data reinforce the importance of abdominal obesity in the etipathogeny of MetS in women with PCOS, thereby constituting, together with HDL concentrations, the parameters conferring a higher relative risk of MetS (25)(26). Only 7% of normal-weight women in our

group of polycystic patients were insulin-resistant. Regarding the degree of insulin resistance, a tendency was observed towards grouping of these patients: those with MetS and two criteria on the one hand and the remaining polycystic patients and a control group on the other. This would confirm the existence of two different PCOS populations: Obese with cardiovascular risk markers and the group of lean or slightly overweight women with no associated metabolic disorders (27). One interesting finding was the absence of differences among basal androgen levels in the different groups, which favors the scant protagonism of these metabolites in the accompanying metabolic disorders.

A highly interesting finding is the great similarity found between patients with MetS and those with only two criteria. In fact, the only significant difference was the presence of higher glucose levels and the high prevalence of women with glucose intolerance and diabetes in the first group that practically trebled that of women with two criteria. Although in the majority of published studies, as in ours, basal glycemia was the less prevalent parameter of those constituting MetS, that does not render it less important. Indeed, this difference reinforces the predictive role of MetS in the later development of glucose metabolism disorders such as an increase in the gestational diabetes rate, more rapid progression from glucose intolerance to diabetes, and that of a higher prevalence of type II diabetes in women with PCOS, as previously observed in our population (28). Thus, it would be recommendable to detect these patients before the glucose metabolism alterations become evident. The main concern here is that awaiting three or more criteria would delay the setting up of preventive measures. The only risk to be run, by widening the diagnosis of MetS with PCOS patients with two criteria, would be to overstimate the risk of cardiovascular disease in these patients, although this does not appear feasible in view of the similarity between groups with two or more MetS criteria. A further valid alternative would be, instead of using a binary definition (MetS present or absent), to be able to calculate a continuous variable of the risk score for a type of syndrome (29).

If, in our population, we had combined waist circumference > 88 cm, HDL < 1.30 mmol/l and triglyceride concentration ≥1.70 mmol/l, we would have a high probability of identifying early PCOS patients with, or susceptible to having, MetS. Both the meeting of experts of Rotterdam

and the Androgen Excess and Polycystic Ovary Syndrome Society (30) recommend the metabolic screening of all obese PCOS patients. If these criteria were applied to our population, up to 20% of women without MetS risk would also have to be studied. Similarly, if waist circumference were used as the only screening parameter and the upper limit were set at 83.5 cm, 57% of patients with one or no MetS criteria would have to be included in the risk population, and if the limit were established at 88 cm, almost 40% of patients without risk would be included. Consequently, other biochemical markers such an uT (16)(34) or the triglycerides/HDL ratio (12) have been added to these clinical parameters as predictors if the existence of MetS. All these parameters are in some way related to the degree of insulin resistance and secondary hyperinsulinism, which constitutes the central axis of glucose metabolism alterations and vascular modifications which will imply a future risk of cardiovascular disease.

In conclusion, the prevalence of MetS in women with PCOS is high compared with the rest of Catalan women, and in a similar range to that of other European countries with obesity, particularly android type, being a determinant factor. The similarity between women with MetS and those with only two factors should lead to them all being considered for measures to prevent the onset of glucose metabolism alterations and later cardiovascular disease. Waist circumference, together with HDL and triglyceride concentrations, constitutes a valid association for selecting PCOS patients as candidates for routine metabolic screening.

Acknowledgments

We are indebted to Christine O'Hara for editing the manuscript and editorial assistance. We also thank Dr. Ignasi Gich from Iberoamerican Cochrane Collaboration for statistical support.

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Figures

Figure 1. Receiver operating characteristic curve for different parameters for separating absence and presence of metabolic risk. AUC, area under the curve; WC, waist circumference; HDL, high-density lipoprotein, TG, triglycerides

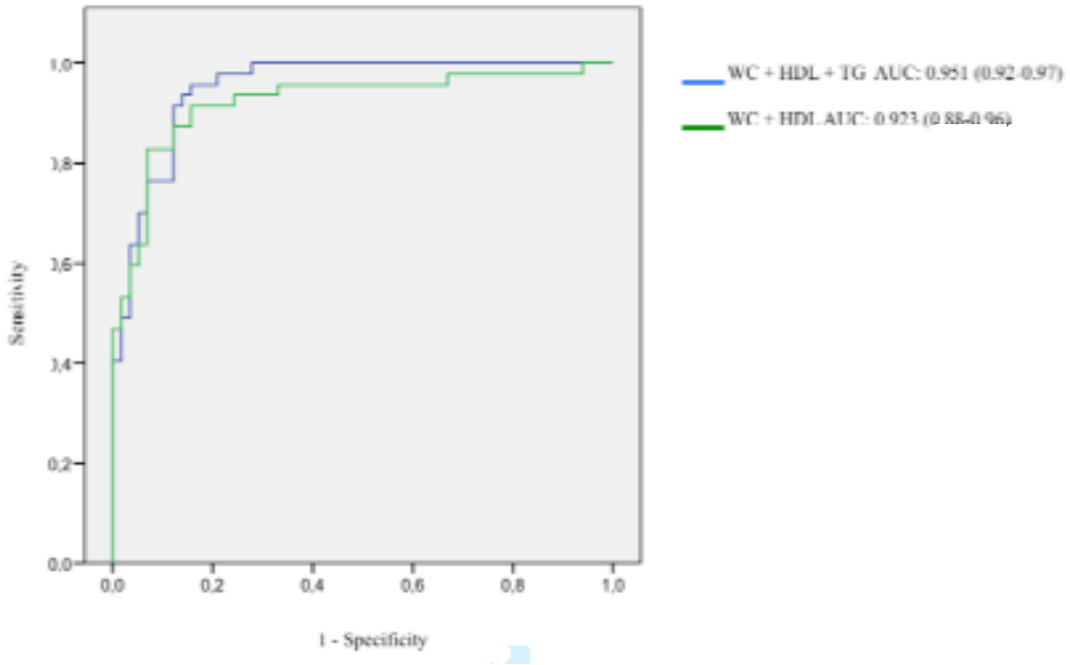

Table 1. Comparison of anthropometric and endocrine characteristics between groups of women with polycystic ovary syndrome according to number of metabolic syndrome criteria present and a control group.

	MetS (n= 42)	Two criteria (n = 64)	One or no criteria (n = 90)	Control group (n = 21)
Age (yr)	27.8±7	26±6	25.6±5	28.5±6
BMI (kg/m^2)	36.5±4^{cd}	33.4±6^{cd}	24,2±7^{ab}	21,6±3^{ab}
Waist (cm)	104.5±26^{cd}	106.5±17^{cd}	87.7±13^{ab}	71.6±7^{ab}
WHR	0.96±0.06	0.93±0.09	0.88±0.08	0.75±0.05
Ferriman-Gallwey score	8.1±5	11.2±5	8.2±4.3	< 8
SBP (mm Hg)	131.1±14^{c}	129.8±19^{c}	104.9±35^{ab}	118.1±16
DBP (mm Hg)	83.3±9^{cd}	79.3±12^{cd}	66.6±23^{ab}	69.4±12^{ab}
LH/FSH	1.4±0.9	1.8±1.5^{d}	1.9±1.2	0.7±0.3^{b}
T (nmol/)	2.2±0.7^{b}	2.8±1^{ad}	2.6±0.9^{d}	1.8±0.6^{bc}
SHBG (nmol/l)	21.2±8^{cd}	31.1±19^{cd}	47.9±29^{abd}	70.1±33^{abc}
uT	11.9±5^{cd}	12±9^{cd}	7.2±4^{abd}	2.8±1^{abc}
Δ4 (nmol/L)	5.7±6.6	6.7±8	6.8±6	6±5.8
17-OHP (nmol/L)	4±3	3.9±1.2	3.7±1.7	3.4±1.5
DHEAS (µmol/L)	1.4±3	1.78±3	1±2.6	2.3±2.4
I (pmol/L)	132.7±60^{cd}	107.8±83^{cd}	61±37^{ab}	41.3±17^{ab}
G (nmol/L)	5.7±1.6^{bcd}	5.08±0.4^{d}	4.99±0.5^{a}	4.8±0.5^{a}
G:I ratio	6.7±3^{d}	10.6±10^{d}	15.1±10	18.2±9^{ab}
QUICKI	0.31±0.02^{cd}	0.33±0.04^{cd}	0.36±0.03^{ab}	0.38±0.02^{ab}
HOMA	4.8±2.9^{cd}	3.6±2.9^{cd}	1.9±1.2^{ab}	1.16±0.6^{ab}

[a] MetS significantly different from the other groups ($p<0.05$)

[b] Two criteria significantly different from the other groups ($p<0.05$)

[c] One or no criteria significantly different from the other groups ($p<0.05$)

[d] Control group significantly different from the other groups ($p<0.05$)

Table 2. Cardiovascular risk factor values by group

	MetS (n= 42)	Two criteria (n = 64)	One or no criteria (n = 90)	Control group (n = 21)
TC (mmol/L)	5.05±1	4.5±1	4.8±0.7	4.6±0.8
LDL (mmol/L)	3.4.±1[d]	3±0.6	2.9±0.6	2.7±0.7[a]
HDL (mmol/L)	1.08±0.1[cd]	1.24±0.3[cd]	1.6±0.3[ab]	1.68±0.3[ab]
VLDL (mmol/L)	0.48±0.2	0.38±0.1	0.69±0.1	0.15±0.09
TG (mmol/L)	1.78±1.7[cd]	1.26±0.8[cd]	0.8±0.03[ab]	0.66±0.2[ab]
Lp(a) (mg/L)	199.5±251	374±353	332±384	274±346
Apo A (g/L)	1.26±0.1[cd]	1.39±0.2[d]	1.5±0.2[a]	1.6±0.2[ab]
Apo B (g/L)	0.95±0.3[cd]	0.84±0.1[d]	0.81±0.1[a]	0.7±0.16[ab]
LDL size (nm)	25.9±0.6	23.6±7	25.4±4	24.9±5.8
CRP (mg/L)	9±9[cd]	5.6±5.7	2.8±4.5[a]	1.7±1.8[a]
Homocysteine (µmol/L)	7.5±1.5[c]	8.4±1.7	9.2±2.6[a]	8.6±2.1

[a] MetS significantly different from the other groups ($p<0.05$)
[b] Two criteria significantly different from the other groups ($p<0.05$)
[c] One or no criteria significantly different from the other groups ($p<0.05$)
[d] Control group significantly different from the other groups ($p<0.05$)