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Prevalence of Type II diabetes mellitus and insulin resistance in parents of women with polycystic ovary syndrome

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Abstract

Aims/hypothesis. Insulin resistance with increased risk of Type II (non-insulin-dependent) diabetes is a common feature of polycystic ovary syndrome (PCOS). To investigate antecedents of metabolic disorders in family members of patients with PCOS, we evaluated glucose tolerance and insulin resistance in parents of patients with PCOS compared to parents of healthy women.
Methods. A total of 200 parents of women with clinical and hormonal evidence of PCOS (PCOSp) and 120 parents of healthy normally cycling women (HWp) were studied. A 75-g OGGT was performed and subjects were classified according to the World Health Organization (WHO) criteria (1999). Serum glucose and insulin were measured before the glucose load and 30, 60 and 120 min after. C-peptide and sex hormone-binding globulin were also determined before the glucose load. Insulin resistance was assessed by HOMA model and ISI composite.
Results. The prevalence of Type II diabetes was 1.89-(1.06–3.38)-fold higher in PCOSp compared to HWp. Insulin resistance, evaluated by $HOMA_{IR}$ and ISI composite was also significantly higher in the PCOSp group compared to the HWp group. After both study groups were distributed by sex, and adjusted by age and BMI, the metabolic parameters were still significantly different between PCOSp and HWp.
Conclusions/interpretation. The data suggest that parents of PCOS women exhibit insulin resistance and Type II diabetes more frequently than those of healthy women, thus constituting a high-risk group but an ideal cohort to detect and prevent the development of Type II diabetes. [Diabetologia (2002) 45:959–964]

Keywords Type II diabetes, polycystic ovary syndrome, insulin resistance, family study.

In recent years, several studies have reported links between insulin resistance and polycystic ovary syndrome (PCOS), one of the most common endocrine disorders affecting 5–10% of the premenopausal women [1, 2, 3, 4]. The most widely accepted definition of PCOS is the association of chronic anovulation and hyperandrogenism in the absence of specific diseases of the ovaries, adrenals and pituitary [5]. In addition, most women with PCOS also have peripheral insulin resistance, affecting predominantly muscle and adipose tissue, and a compensatory hyperinsulinaemia independent of obesity [3, 6, 7, 8, 9]. At present, it is accepted that insulin resistance and pancreatic beta-cell dysfunction, with increased risk of Type II diabetes mellitus, are usual comorbilities in PCOS patients [10, 11, 12]. Studies have shown that 25–35% of obese women with PCOS will have either impaired glucose tolerance or Type II diabetes by 30 years of age, and that the history of Type II diabetes in a first-

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Abbreviations: PCOS, Polycystic ovary syndrome; $HOMAR_{IR}$, homeostasis model assessment for insulin resistance; ISI, whole-body insulin sensitivity; SHBG, sex hormone-binding globulin; FAI, free androgen index.

degree relative define a subset of PCOS subjects with a greater prevalence of insulin secretory defects [13, 14]. Therefore, PCOS is a major women´s health issue with implications well beyond the reproductive endocrine abnormalities that usually bring women with PCOS to clinical attention in early ages. This offers the opportunity to detect metabolic abnormalities earlier in these women [10, 15].

In view of the high prevalence of affected individuals, a genetic cause of the syndrome was suggested many years ago [16]. This has been investigated in several studies on PCOS phenotypes in different populations [17] and in family studies which indicated that a high number of female relatives are affected [18, 19, 20, 21]. Most of these studies have used ovarian morphology [22, 23] and endocrine abnormalities such as hyperandrogenaemia and anovulation to assign affected status [24]. However, the antecedents of metabolic disorders in family members of PCOS patients has not been widely studied. One study suggests that there are increased insulin concentrations among first-degree relatives of PCOS patients [25] and another that there is a heritable component to beta-cell dysfunction in families of women with PCOS [26]. In a recent study our group obtained from the clinical history and personal interviews with healthy women, PCOS patients and their parents and found that the probability of finding Type II diabetes in family members (brothers, parents and grandparents) of PCOS patients was significantly higher than in the control group [27]. In order to confirm the observations noted in the interviews, this study was designed to evaluate glucose tolerance, insulin resistance and frequency of Type II diabetes in parents of healthy women and of PCOS cases.

Subjects and methods

This is a case control study designed with a familial component (family study) [28].

Subjects. Altogether 106 unrelated women with PCOS, with an age range of 15–35 years, were consecutively recruited from patients attending the Unit of Endocrinology and Reproductive Medicine, University of Chile between 2000–2001.

Diagnosis of PCOS was made if subjects had chronic anovulation, hyperandrogenism without any other specific causes of adrenal or pituitary disease and met the diagnostic criteria for PCOS of the NIH consensus [5].

Inclusion criteria for cases were: chronic oligo- or amenorrhoea, hirsutism, plasma total testosterone concentration of more than 0.6 ng/ml or free androgen index (FAI) of less than 5.0. All women were amenorrhoeic and anovulatory according to progesterone measurements and ultrasound examination. Characteristic ovarian morphology as detected by ultrasound was not considered an inclusion criterion. Hyperprolactinaemia, androgen secreting neoplasm, Cushing's syndrome and attenuated 21-hydroxylase deficiency, as well as thyroid disease, were excluded by appropriate tests.

Sixty healthy women (HW), with normal cycles between 15 and 35 years old (Table 1), acted as a control group. Each one had a history of regular 28- to 32-day menstrual cycles, absence of hirsutism and other manifestations of hyperandrogenism, and absence of galactorrhoea and thyroid dysfunction. They had normal hormonal status, were not receiving oral contraceptives or any drug therapy for at least 6 months before starting the study and had the antecedent of a normal term pregnancy with vaginal delivery of a healthy infant. Since PCOS can be diagnosed even in women with regular menses [29], only women with the antecedent of a normal term pregnancy were selected for the control group, in order to reduce a possible misleading effect of an inaccurate disease classification. The women of the control group were recruited from the same city area as the patients.

Table 1. Clinical and metabolic characteristics of healthy (HW) and PCOS women (PCOS)

	HW (n = 60)	PCOS (n = 106)
Age (years)	26.66 ± 6.25	22.63 ± 6.72[a]
BMI (kg/m^2)	26.16 ± 3.67	29.80 ± 7.20[a]
Waist diameter (cm)	85.20 ± 10.09	90.99 ± 17.21
SHBG (nmol/l)	58.75 ± 28.55	29.62 ± 22.58[a]
Testosterone (ng/ml)	0.35 ± 0.12	0.81 ± 0.41[a]
FAI	2.30 ± 1.16	14.62 ± 11.71[a]

[a] $p < 0.01$ adjusted by age
The values are means ± SD

PCOS patients and control women were included in the study regardless of their family history of diabetes in first-degree relatives.

A total of 200 parents of PCOS cases (PCOSp) and 120 parents of healthy women with normal cycles (HWp) were enrolled for a family study in which a detailed evaluation of Type II diabetes, glucose tolerance and insulin resistance was carried out.

All subjects had given their written consent to their participation in the study which was approved by the local ethics committee.

Study protocol. After a 3-day 300-g carbohydrate diet and an overnight fast of 10 h, both groups of women and their parents were admitted to the Clinical Research Centre in the morning (8:30–9:00 h). A clinical history was obtained and a physical examination was conducted. A 75-g OGTT was done and subjects were classified according to the World Health Organization (WHO) criteria (1999) [30]. Serum glucose and insulin were measured before the glucose load and 30, 60 and 120 min after. C-peptide and sex hormone-binding globulin (SHBG) were also determined before the glucose load.

Data analysis. The measurements derived from the OGTT included the following: i) serum fasting glucose, serum fasting insulin and serum fasting C-peptide; homeostasis model assessment for insulin resistance ($HOMA_{IR}$) according to a previous study [31] and whole-body insulin sensitivity (ISI composite) [32]; ii) serum 2-h glucose and 2-h insulin; iii) area under the curve of glucose (Glucose AUC) and insulin (Insulin AUC).

Assays. Serum glucose was determined by the glucose oxidase method (Photometric Instrument 4010; Roche, Basel, Switzerland). The coefficient of variation of this method was less than 2.0%. Serum insulin and C-peptide were assayed by RIA (DPC, Los Angeles, Calif., USA) and SHBG by radioimmunometric assay (DPC, Los Angeles, Calif., USA). The intra-assay and inter-assay coefficients of variation were 5% and 8% for insulin; 3.4% and 7.2% for C-peptide and 3.8% and 7.9% for SHBG.

Statistical analysis. Firstly, case-control comparisons for the prevalence of Type II diabetes and the family history of Type II diabetes were evaluated. Secondly, the statistical analysis focused on the sex-specific comparisons between two groups comprising parents of PCOS and parents of healthy women, respectively. Categorical data were analysed using chi-square (χ^2) test, prevalence ratio and 95%-CI. Differences in continuous data (expressed as means ± SD) were analysed using multivariate analysis (multiple linear regression techniques). A p value of less than 0.05 was considered to be statistically significant.

Results

Case- control comparisons. Table 1 shows the clinical and hormonal characteristics of healthy and PCOS women. BMI was different between both groups ($p < 0.01$). Mean age was lower in PCOS women compared to HW women ($p < 0.01$). The introduction of a normal-term pregnancy in the inclusion criteria of the control group could explain the age differences between both groups. After the different parameters were adjusted by age, total serum testosterone concentrations and free androgen index (FAI) were higher and SHBG concentrations were lower in the PCOS group.

The prevalence of Type II diabetes and impaired glucose tolerance (IGT) in these PCOS women was 4.6% and 9.3%, respectively. No cases of Type II diabetes or IGT were detected in the control group.

According to the data obtained from the interview, the frequency of Type II diabetes was higher in the family history of PCOS cases compared to that of the control group ($p = 0.045$). In the PCOS group, nine patients had the antecedent of two parents with Type II diabetes. (Table 2). These diabetic parents were all under treatment with diet and oral drugs.

Table 2. Family history of Type II diabetes for controls and PCOS cases

Parents	HW ($n = 60$)		PCOS ($n = 94$)[a]		p
	n	%	n	%	
0	47	78.3	65	69.1	
1	13	21.7	20	21.3	0.045
2	–	–	9	9.6	

[a] Twelve PCOS cases were not included in the table due to the fact that one of the parents was absent

Table 3. Prevalence of Type II diabetes in groups of parents

	HWp ($n = 120$)		PCOSp ($n = 200$)		p
	n	%	n	%	
Non Type II diabetes	107	88.96	149	79.50	0.025
Type II diabetes	13	10.83	41	20.50	

Using the WHO criteria (1999), considering a fasting serum glucose ≥126 mg/dl and OGTT with a 2-h post load value ≥200 mg/dl

Parents comparisons. In relation to the clinical characteristics of both groups of parents, the BMI values for the parents of PCOS women (29.46 ± 4.80) and the parents of healthy women (28.30 ± 4.30; $p < 0.025$) were different. The parents of healthy women were older than those of PCOS women (54.83 ± 9.95 vs 50.44 ± 7.46; $p < 0.05$).

Table 3 shows the prevalence of Type II diabetes in PCOS parents and parents of healthy women according to WHO criteria (1999).

The prevalence of Type II diabetes was significantly higher in PCOS parents compared to HW parents ($p = 0.025$). Prevalence ratio for Type II diabetes in PCOS parents versus HW parents was 1.89 (95%-CI 1.05; 3.38).

Impaired glucose tolerance was similar in parents of healthy women and parents of PCOS women (HW parents: 20.83%; PCOS parents: 19.00%). Diabetes was detected in most parents based on fasting values and impaired glucose tolerance based on 2-h glucose challenge. In the absence of unequivocal hyperglycaemia, fasting glucose values were tested on a different day.

Comparing the prevalence of Type II diabetes obtained from the clinical history (Table 2) and glucose determinations (Table 3) shows that the prevalence of diabetes in both conditions was significantly higher in PCOS parents than in parents of healthy women.

Table 4 shows the clinical characteristics of PCOS and HW diabetes-free parents distributed by sex. Both

Table 4. Clinical characteristics of healthy (HWp) and PCOS (PCOSp) diabetes-free parents distributed by sex

	HWp		PCOSp	
	Fathers ($n = 52$)	Mothers ($n = 55$)	Fathers ($n = 74$)	Mothers ($n = 85$)
Age (years)	56.48 ± 10.66	53.12 ± 9.55[b]	52.64 ± 8.64[a, b]	47.95 ± 7.09[a]
BMI (kg/m^2)	27.50 ± 3.88	28.71 ± 4.90	29.26 ± 4.21[a]	29.00 ± 5.38

[a] $p < 0.05$ between HWp and PCOSp; [b] $p < 0.05$ between fathers and mothers; Values are means ± SD

Table 5. Metabolic parameters of healthy (HWp) and PCOS (PCOSp) diabetes-free parents distributed by sex and adjusted by age and BMI

	HWp		PCOSp	
	Fathers (n = 52)	Mothers (n = 55)	Fathers (n = 74)	Mothers (n = 85)
Fasting				
Glucose (mg/dl)	90.67 ± 14.81	89.37 ± 14.69	93.02 ± 15.08[b]	86.58 ± 13.07
Insulin (µUI/ml)	12.23 ± 6.92	10.85 ± 8.57	16.46 ± 12.56[b]	12.40 ± 8.21
C-Peptide (ng/ml)	1.41 ± 0.86	1.33 ± 0.74	2.07 ± 0.80[a, b]	1.81 ± 0.73[a]
SHBG (nmol/l)	50.84 ± 30.29	50.47 ± 24.02	30.25 ± 15.08[a]	48.04 ± 20.83
$HOMA_{IR}$	2.45 ± 2.00	2.82 ± 1.82	3.89 ± 3.30[b]	2.68 ± 1.88
2 h				
Glucose (mg/dl)	107.03 ± 33.06	112.75 ± 36.83	110.08 ± 33.35	112.75 ± 33.97
Insulin (µUI/ml)	58.71 ± 53.80	58.76 ± 46.25	90.86 ± 88.47	70.43 ± 53.00[a]
Glucose (AUC)	15259.2 ± 3705.8	15286.3 ± 4434.3	16478.3 ± 3886.0[b]	14984.0 ± 3855.2
Insulin (AUC)	7237.1 ± 4787.1	7996.4 ± 6407.4	11326.5 ± 8395.1[a, b]	8631.8 ± 6663.1
$ISI_{composite}$	5.70 ± 4.48	6.46 ± 4.69	4.20 ± 3.40[b]	5.12 ± 2.82[a]

Values are means ± SD; [a] $p < 0.05$ between HWp and PCOSp; [b] $p < 0.05$ between fathers and mothers

parents of PCOS patients were younger than those of healthy women. BMI was higher in PCOS fathers compared to fathers of healthy women. The BMI of the mothers was similar.

After each metabolic parameter was adjusted for age and BMI (Table 5), C-peptide and SHBG concentrations and AUC insulin were different between PCOS fathers and fathers of healthy women. The mothers also showed differences in serum concentrations of C-peptide and 2-h insulin and in insulin sensitivity evaluated by ISI composite ($p < 0.05$).

Comparing the fathers with the mothers of both groups after the data were adjusted by age and BMI, the PCOS fathers showed higher fasting glucose, insulin and C-peptide concentrations, AUC glucose and AUC insulin, and insulin resistance evaluated by HOMA IR and ISI-composite than the PCOS mothers. The fathers of healthy women did not show any differences compared with the mothers (Table 5).

Discussion

In this study, we confirmed our previous observation, based on data obtained from the clinical history and personal interview, that the parents of PCOS women had Type II diabetes more frequently than those of healthy women. Age was not the explanation for the differences observed in our study. Eligibility criteria for the control group included healthy women with the antecedent of a normal term pregnancy. Therefore, the healthy women were older than the PCOS women and, consequently, the parents of the healthy women were older than those of the PCOS women. Given the fact that the approximate mean age for Type II diagnosis is around 60 years [33], our observation of a higher prevalence of such disorder in parents of PCOS women compared to parents of healthy women would add additional strength to the hypothesis of an important family clustering of PCOS and Type II diabetes.

In contrast to Type II diabetes, impaired glucose tolerance was similar in parents of healthy women and in those of PCOS patients, suggesting that in this latter group the passage from impaired glucose tolerance to Type II diabetes is likely to be more premature, possibly reflecting the presence of a pancreatic beta-cell dysfunction as previously suggested for PCOS patients [13, 27, 34]. On the other hand, Type II diabetes was detected in most PCOS parents based on fasting values. This observation is important because it means that the diagnosis of diabetes, in this group, could be established by fasting glucose values. However, impaired glucose tolerance was detected mostly based on 2-h glucose challenge values. This means that, to detect and prevent the development of Type II diabetes in this group, the oral glucose tolerance test offers more advantages than a fasting value alone. In PCOS patients, fasting glucose concentrations are poor predictors of Type II diabetes [35], probably because these patients are too young and have a less severe form of glucose intolerance. As for the general population [36], in these patients glucose tolerance tends to worsen with age in an accelerated manner [18]. Further follow-up studies are needed to confirm this observation in parents of PCOS patients.

Several methods have been proposed to evaluate insulin sensitivity from data obtained by the OGTT. Most of them rely on the ratio of plasma glucose to insulin concentrations during the OGTT. In this study we chose the $HOMA_{IR}$ [31] and ISI composite [32] methods which are simple to calculate, provide a reasonable approximation of whole-body insulin sensitiv-

ity, and can be applied to the study of a high number of subjects. In patients with hyperinsulinaemic insulin resistance, the circulating concentrations of SHBG are lower due to the inhibitory effect of insulin on hepatic SHBG production [37, 38] and, therefore, circulating SHBG concentrations could be useful as biological markers for hyperinsulinaemic insulin resistance [39, 40] and as a risk factor for the development of Type II diabetes [41]. In this context, it is interesting to point out that PCOS fathers showed significantly lower concentrations of SHBG than fathers of healthy women, and PCOS mothers had lower insulin sensitivity than mothers of healthy women.

Thus, metabolic abnormalities, related to insulin resistance, evaluated through different parameters, were detected more frequently in both parents of PCOS women independent of body weight. The presence of insulin resistance in early ages in the parents of PCOS women, could be the first step in the development of Type II diabetes. Therefore, its detection and the employment of therapeutical tools could be of utility in the prevention of this disorder. On the other hand, the presence of metabolic abnormalities in both parents could provide a higher genetic load and might explain the high prevalence of Type II diabetes in these patients.

Fathers of PCOS women were more obese than those of healthy women. This phenomenon could be related either to environmental factors, such as eating habits, or to genetic conditions. However, mothers of PCOS women exhibited a BMI similar to mothers of healthy women, therefore, it is not very likely that the family dietary habits could account for the higher BMI of the PCOS fathers. On the other hand, it has been described that sisters of PCOS patients have higher BMI than sisters of normal women, thus suggesting a genetic component in PCOS-associated obesity in these subjects [24]. After being corrected by BMI, PCOS fathers had metabolic alterations more frequently than those of healthy women. In this group, obesity clearly provoked a worsening of hyperinsulinism and insulin resistance.

Fathers of PCOS women show metabolic alterations more frequently than mothers; it has been previously suggested that the inheritance of PCOS could be preferentially paternal, based on the rates of PCOS in mothers and sisters of PCOS patients [42, 43]. At the moment, we have no explanation for this observation. Nevertheless, if PCOS does have a genetic component, then males must carry the susceptibility genes as well. In males from families with PCOS, an increase in the prevalence of premature male-pattern balding has led investigators to suggest that premature male-pattern baldness is the male phenotype of the disease [23, 44, 45]. However, no evidence of hyperandrogenaemia has been established in PCOS brothers or fathers with premature male-pattern balding. Therefore, insulin resistance could be a better phenotype to search for in males with premature male-pattern balding as previously suggested [46], especially in those from PCOS families.

Current recommendations of the American Diabetes Association indicate that Type II diabetes screening programs should be routinely carried out in subjects over 45 years old in a universal manner. However, some authors have suggested that this strategy is inefficient and propose a targeted search for new cases in high-risk groups [47]. In this context, PCOS parents constitute a high-risk group, due to the fact that they are more insulin resistant and have Type II diabetes more often and before the expected time than in the general population. Therefore, in the authors' opinion, they should also be screened for these abnormalities.

In summary, parents of PCOS women constitute a high- risk group but an ideal group to detect and prevent the development of Type II diabetes and its complications. Moreover, the fathers are apparently at higher risk than the mothers.

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