A survey of metabolic syndrome in first-degree relatives (fathers) of patients with polycystic ovarian syndrome

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Abstract

Objectives: Women with polycystic ovarian syndrome (PCOS) are at twice the risk of developing metabolic syndrome, compared to women from the general population. The aim of this study was to assess the prevalence of metabolic syndrome in the first-degree relatives (fathers) of patients suffering from PCOS.

Design: This was a case control study.

Setting and subjects: The study was conducted on 34 fathers of women with PCOS who presented at gynaecological clinics in Shiraz, Iran (as the case group), and 34 fathers of healthy women (as the control group).

Outcomes measures: Metabolic syndrome was determined according to Adult Treatment Panel III (ATP III) and International Diabetes Federation (IDF) indices. A blood sample was obtained to assay serum insulin, blood sugar, testosterone and lipoproteins. The data were analysed using independent t-test, Fisher's exact test and the chi-square test.

Results: According to the ATP III index, the prevalence of metabolic syndrome was 29.35% in the fathers of the PCOS patients and 8.8% in the fathers of women in the control group (p-value < 0.05). According to the IDF index, this rate was 17.41 in the fathers of patients with PCOS (p-value < 0.05). According to the quantitative insulin sensitivity check and homeostasis model insulin resistance indices, the prevalence of insulin resistance, hypertension, type 2 diabetes and hypercholesterolaemia was higher in the fathers of patients with PCOS than in the control group, but the difference was not significant (p-value > 0.05).

Conclusion: The fathers of the women with PCOS were at a higher risk of developing metabolic syndrome, hypertension, dyslipidaemia, impaired glucose tolerance and diabetes.

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Introduction

One of the most common disorders that affects women is polycystic ovarian syndrome (PCOS). The classic form of this syndrome includes amenorrhoea, anovulation, infertility, hirsutism, obesity and enlarged bilateral ovaries with cysts.[1] Obesity has been found in at least 50% of women with PCOS. These patients usually have central (android) body fat distribution. Android obesity, which is characterised by an increased waist-to-hip ratio (> 0.80), leads to an increased risk of diabetes mellitus and cardiovascular disease.[2] One study showed that the prevalence of obesity in women with PCOS increased from 51% between 1987 and 1990 to 74% between 2000 and 2002.[3] In addition, insulin resistance and hyperinsulinaemia commonly occur in patients with PCOS. In these cases, the rate of IGT and diabetes mellitus type 2 is 16-35% and 5-17%, respectively. These rates slightly increase, even in non-obese women, with PCOS.[3]

In addition, insulin resistance and hyperinsulinaemia commonly occur in patients with PCOS. In these cases, the rate of IGT and diabetes mellitus type 2 is 16-35% and 5-17%, respectively. These rates slightly increase, even in non-obese women, with PCOS.[25]

Lipoprotein abnormalities are also common in PCOS. Disorders that relate to lipoprotein abnormalities include elevated levels of total cholesterol, triglycerides and low-density lipoprotein (LDL), as well as decreased levels of high-density lipoprotein (HDL) and apolipoprotein AI. Other observations in women with PCOS include an increased incidence of hypertension over time to a rate of 40% around menopause, a higher incidence

of atherosclerosis and cardiovascular disease, and increased risk of myocardial infarction. Other PCOS complications include sleep apnoea and infertility.[2] The high familial incidence of the disease suggests its genetic origin, but there is limited information on the involved gene or genes.[4] This disease is among the most significant causes of mortality. The risk of developing atherosclerotic cardiovascular disease[5] and type 2 diabetes mellitus is likely with metabolic syndrome.[6] Moreover, coronary artery disease accounts for nearly 50% of all yearly deaths in Iran.[7]

The prevalence of PCOS varies from 4-10%,[8-10] up to 17-22%,[11-12] depending on the criteria used.

Since no studies have been conducted on this issue in Iran, this study was designed to investigate the rate of metabolic syndrome in the fathers of patients with PCOS presenting at gynaecology clinics in Shiraz, Iran.

Method

Patients with clinical PCOS were identified. Their fathers, aged 30 years and older, who met the inclusion criteria of the study, were interviewed and the first part of a questionnaire, which included demographic information, was completed. Individuals who fulfilled the inclusion criteria of the study and who provided written informed consent to take part in the research were considered to constitute the experimental group. The control group included fathers of women with no history of PCOS, nor no history of it in their families. A full history, which included information on the regularity of menstrual periods and records of hirsutism and infertility, was obtained. Women were included in the study as controls if they met the inclusion criteria of not smoking, having no history of PCOS, being over 30 years old, and not using drugs to control blood sugar, blood lipids and blood pressure, as well as free testosterone.

In this study, 17 brothers and 34 fathers were selected as the case group. Thirty-four fathers were chosen as the control group according to the insulin index[13] and the following formula:

$$N = \frac{4(Z_{\alpha/2} + Z_{\beta})^2 \delta^2}{d^2}$$

Blood pressure, body mass index (BMI) and the waist-hip index were measured in both groups. The subjects' weight was determined when wearing minimum clothing and no shoes, using digital scales, with minimum error of approximately 100 g. In addition, their height was measured while in a standing position, without shoes, using a tape measure. BMI was calculated by dividing the weight in kilogrammes by the squared height in metres. BMI ≥ 18.5 kg/m^2 and < 25 kg/m^2 was considered to be normal, 25-29.9 kg/m^2 overweight, 30-34.9 kg/m^2 obese (class I), 35-39.9 kg/m^2 obese (class II), and ≤ 40 kg/m^2 obese (class III).[14-15]

Waist-to-hip index was also determined while standing. The waist circumference was measured from the lowest rib margin and iliac crest (umbilical area) at the end of exhalation and the hip circumference over the widest area of the gluteal region (the widest femoral circumference). If the ratio of these two measurements (waist to hip) was more than 0.85 in women and 0.9 in men, it was considered to constitute central obesity (android obesity).[16]

After 15 minutes, blood pressure was measured by means of a sphygmomanometer matched to the arms diameter while the patients were sitting on a chair with no cover, with their right arms at a 45-degree angle to their chests and their elbows matched to the arm's diameter. The bag pressure gauge was tied 2.5 cm above the elbows. Blood pressure was measured twice from the right arm with a 10-minute interval and its mean was recorded as the blood pressure. Blood pressure that was equal to, or higher than, 140/90 mmHg was diagnosed as hypertension.

Before testing, patients were reminded not to use drugs that might affect their blood sugar and blood pressure, including acetaminophen, benzodiazepines and beta blockers, oral contraceptive pills, phenytoin or thiazide diuretics, the night and the morning before the tests. Overnight fasting of 12-10 hours before the test was necessary for participants.

Blood samples were obtained from participants between 7h00 and 9h00, and the samples centrifuged according to standard protocols 30-45 minutes later. To perform the oral glucose tolerance test, 75 g monohydrate glucose, soluble in water, was administered orally to the participants. Fasting blood glucose, fasting insulin, free blood testosterone, triglycerides, total cholesterol, and LDL and HDL were also measured in the subjects. Serum was used to gauge insulin. However, since insulin is only stable at -8°C for 2-24 hours, a freezer with a temperature of -70°C was used to store it over the long term. After collecting the samples, insulin was measured using the radioimmunoassay method and the Mercodia kit (Sweden). Based on this kit, the natural insulin level was considered to be 2-25 MIU/l. Fasting blood glucose, triglycerides, cholesterol and testosterone were measured according to the calorimetrically enzymatic method, using Pars test kits (Tehran, Iran). HDL and LDL levels were also analysed using the immunoturbidometry test (Pars, Iran) method utilising a joint device. Triglycerides ≥ 150 mg/dl, HDL < 40 mg/dl in males, HDL < 50 mg/dl in females, and LDL ≥ 160 mg/dl were considered to be abnormal results. Fasting blood glucose tests and two-hour blood sugar

(oral glucose tolerance test) were assessed according to World Health Organization (WHO) criteria.

Impaired glucose tolerance (IGT) was evaluated using the following criteria:[17]

Glucose intolerance: > 140 mg/dl and < 200 mg/dl .
Diabetes mellitus: > 200 mg/dl.
Fasting plasma glucose: > 100 and < 126 mg/dl.
Diabetes mellitus: fasting glucose > 126 mg/dl.

To assess insulin resistance, homeostasis model insulin resistance (HOMA) and quantitative insulin sensitivity check index (QUICK) indices were used. The HOMA index was devised by Mato et al in 1985.

Fasting plasma glucose and fasting insulin levels were calculated according to the following formulas:[18-23]

HOMA = [fasting insulin (μU/ml) fasting glucose (mmol/l)]/22.5.
HOMA = [fasting insulin (mU/l) x fasting glucose (mg/dl)/405.

In 2000, a new index, QUICK, was devised by Katz et al to assess insulin sensitivity and which had a better correlation with direct standard methods than the HOMA index.

This index was also calculated by using glucose and fasting insulin serum:

QUICK = 1/[log fasting insulin(μU/ml)+ log fasting glucose in (mg/dl)].

The subjects with HOMA ≥ 2.38, QUICK ≤ 0.33, or fasting insulin ≥ 10.58 (μU/ml), were considered to be insulin resistant.[24-25]

In this study, Adult Treatment Panel III (ATP III), International Diabetes Federation (IDF) and HOMA criteria were used to investigate metabolic syndrome.

According to the ATP III index, the diagnostic criteria for metabolic syndrome are listed below. Having three of the following disorders equates to a diagnosis of metabolic syndrome:

- *Abdominal obesity (waist circumference):* Men >102 cm and women > 88 cm.
- *Blood pressure:* ≥ 130/≥ 85 mmHg.
- *Triglycerides:* ≥ 150 mg/dl.
- *HDL cholesterol:* Men < 40 mg/dl and women < 50 mg/dl.
- *Fasting glucose:* ≥ 110 mg/dl.[26]

According to the IDF index, the diagnostic critera for metabolic syndrome are as follows:

- *Abdominal obesity (waist circumference):* Men > 90 cm and women > 80 cm.
- *Blood pressure:* ≥ 130/≥ 85 mmHg.
- *Triglycerides:* ≥ 150 mg/dl.
- *HDL cholesterol:* Men < 40 mg/dl and women < 50 mg/dl.
- *Fasting glucose:* ≥ 100 mg/dl.[27]

P-values less than 0.05 were considered to be statistically significant.

According to the tests results, subjects with insulin resistance, abnormal glucose intolerance, elevated testosterone, high LDL and triglycerides, low HDL or high blood pressure were identified, provided with individual counselling and referred to an endocrinologist for further examination.

Results

In this study, no statistically significant difference was found between the two groups with regard to age (p-value < 0.05). According to the ATP III criteria, the

Table I: Distribution of insulin resistance in the fathers according to the homeostasis model insulin resistance index, quantitative insulin sensitivity check index, and insulin fasting index, in the study population

Frequency group	Controls, n = 34				Experimental, n = 34			
	IR		Without IR		IR		Without IR	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
According to HOMA index	2	5.8	32	94.11	5	14.7	29	85.3
According to QUICK index	2	8.82	31	91.77	7	20.6	27	79.4
According to IF index	1	2.94	33	97.05	4	11.76	30	88.23

HOMA: homeostasis model insulin resistance, IF: insulin fasting, IR: insulin resistance, QUICK: quantitative insulin sensitivity check

Table II: Comparison of metabolic syndrome in the fathers of women with polycystic ovarian syndrome and the controls

Group metabolic syndrome	Experimental, n = 34 Metabolic syndrome		Controls, n = 34 Metabolic syndrome		Statistical value
	Number	Percentage	Number	Percentage	
Metabolic syndrome according to ATP III indices	12	35.29	3	8.8	0.008
Metabolic syndrome according to IDF indices	14	41.17	4	11.76	0.007

ATP III: Adult Treatment Panel III, IDF: International Diabetes Federation

Table III: Comparison of diabetes, blood pressure and cholesterol incidence in the experimental and control groups

Group complication	Experimental, n = 34		Controls, n = 34		Statistical value
	Number	Percentage	Number	Percentage	
Type 2 diabetes	10	29.4	3	8.8	0.06
Hypertension	5	14.7	2	5.8	0.04
High cholesterol	6	17.6	3	8.8	0.6

Furthermore, LDL levels were increased in the fathers of the case group, compared to those in the control group. However, the difference was not statistically significant (p-value = 0.6).

rate of metabolic syndrome was 35.29% and 8.8% in the fathers of women with PCOS and in the controls, respectively. A fourfold increase was observed in the case group in terms of the risk of having metabolic syndrome. According to the IDF diagnostic criteria, the incidence of metabolic syndrome was 41.17% in the case group, and 11.76% in the controls, and the difference was statistically significant (p-value < 0.05).

Glucose intolerance and blood pressure were higher in the fathers of the case group, compared to the control group, and the difference was statistically significant (p-value < 0.05). According to the HOMA and QUICK indices, insulin resistance in the relatives of women with PCOS was higher than it was in the controls (p-value ≥ 0.05). Also, fasting insulin was higher in the case group than it was in the control group. However, the difference was not statistically significant (p-value ≥ 0.05) (Tables I-III).

Discussion

PCOS is one of the most common endocrine disorders affecting premenopausal women. The prevalence of this disorder varies from 4-12% worldwide. Metabolic syndrome is defined by metabolic indices, such as abdominal obesity (central obesity), insulin resistance, elevated blood glucose, dyslipidaemia and hypertension. Patients suffering from metabolic syndrome are at high risk of developing cardiovascular disease.[28] According to the WHO and IDF, metabolic syndrome is associated with a 2.69 (2.45-2.95) and 2.20 (2.03-2.38) increase, respectively, in the risk of myocardial infarction.[29] In comparison to normal men and women, patients with metabolic syndrome are at greater risk (127%) of acquiring cardiovascular disease and having strokes, ischaemic heart disease and diabetes.[30] According to studies conducted in Turkey in recent years, the first-degree relatives of patients with PCOS are an at-risk group.[31] Nevertheless, to the best of our knowledge, no Iranian studies have been performed in this field.

Thus, the present study was designed to determine the incidence of metabolic syndrome in the first-degree relatives (fathers) of patients with PCOS. According to the ATP III criteria, the rate of metabolic syndrome was four times higher in the case group fathers compared to the control group, and the difference was statistically significant (p-value = 0.008). According to the IDF criteria, the rate of metabolic syndrome was significantly higher in the fathers of the experimental group than in the controls (p-value = 0.007). Similar results were also obtained in other studies that addressed this issue.

In a study conducted by Benitz, the incidence of metabolic disorders was 62.5% in the first-degree relatives of patients with PCOS, and 27.8% in those of subjects in the control group (p-value < 0.05).[13]

Metabolic syndrome is highly prevalent worldwide and 10-20% of non-diabetics suffer from this syndrome.[32] The results of the study by Camacho indicated that 23.7% of American adults were affected by this syndrome.[33] Moreover, in Covielli's study, the incidence of the disorder was 42% in the relatives of patients with PCOS versus 32% in the relatives of subjects in the control group.[34] In another study, the incidence was estimated to be 40% in men and 29% in women.[35]

Shiwaku conducted a study to determine the prevalence of metabolic syndrome in workers from Japan, Korea and Mongolia using the ATP III criteria.[36] The incidence of this syndrome was approximately 13%, 14%, and 19% in Japanese, Korean, and Mongolian men, respectively. Also, the prevalence of metabolic syndrome was approximately 12%, 12%, and 14% in Japanese, Korean and Mongolian women, respectively.[36]

Mortality from heart disease and diabetes is higher in patients with this disorder than it is in the normal population.[37]

Metabolic syndrome may be viewed as a bridge between diabetes and heart disease because approximately 50% of patients with type 2 diabetes suffer from metabolic syndrome. Therefore, they are more likely to suffer from disorders such as strokes, retinopathy and neuropathy, and to have microalbuminuria.[38]

To evaluate the agreement between the ATP III and IDF methods of diagnosing metabolic syndrome, the Kappa test was used. The results revealed significant agreement between the two methods (kappa = 81.5%).

The average fasting blood glucose in the fathers of the control group was lower than that in the experimental

group (p-value < 0.05). Our results were similar to those reported by Sir-Petermann et al. In that study, the mean of fasting blood sugar was higher in the fathers of women with PCOS than it was in the fathers of the healthy women (controls).[39] Similar results were obtained by Benitz et al.[13]

According to the WHO criteria, the rate of IGT was 5.8% in the fathers of the control group (n = 2) and 26.7% in the experimental group (n = 9) and the difference was considered to be statistically significant (p-value = 0.04). In other studies, the rate of IGT was 31% in the fathers of the group with PCOS; significantly higher than that in the first-degree relatives of the control subjects (p-value < 0.05).[39-41] In a Turkish study, 52% of the fathers of the women with PCOS, and 15% of the control group fathers, had IGT (p-value < 0.05).[40]

In a study by Yilmaz et al, the prevalence of diabetes mellitus, IGT, and impaired fasting glucose was 17.5%, 17.5% and 5%, respectively, in mothers with PCOS, and 21%, 28% and 5% in the fathers. Overall, the control group had 15% IGT. The difference between the first-degree relatives of the patients with PCOS and those of the control group was found to be statistically significant (p-value < 0.001).[42]

Kang et al stated that glucose intolerance was one of the modifiable risk factors for diabetes.[41] Approximately 50-70% of women with PCOS, and 80-100% of patients with type 2 diabetes mellitus, had variable degrees of insulin resistance. Also, women with PCOS had a 5-10 times higher risk of developing diabetes, compared to their matched controls.[43]

In this study, the mean total cholesterol in the case group was significantly higher than that in the control group (p-value = 0.001), which is consistent with the results obtained in another study performed in the endocrinology section of Chil University.[36] In that study, the fathers of women with PCOS had higher total cholesterol than the fathers of the healthy women (p-value < 0.05).[44]

Sir-Petermann et al conducted a study at the University of Chil in Santiago to investigate glucose tolerance and insulin resistance in the parents of patients with PCOS, compared to that in the parents of healthy women.[39] According to the results, the incidence of type 2 diabetes was 1.89-fold higher in the parents of patients with PCOS than it was in the control group. Insulin resistance was also significantly higher in the parents of the women with PCOS, compared to the control group. A significant difference was also observed between the two groups with regard to metabolic parameters.[39] Based on the results of clinical studies conducted on the issue, the development of diabetes can be prevented by maintaining proper sugar levels.[45]

In the current study, hypertension was diagnosed in 5.8% (n = 2) of the control group and in 14.7% (n = 5) of the experimental group, and the difference was considered to be statistically significant (p-value = 0.04). In the study by Benitz et al, the incidence of hypertension was also significantly higher in the fathers of the women with PCOS, than it was in the control group (9.3% vs. 18.7%) (p-value < 0.05).[13] In the current study, hypertension was diagnosed in 5.8% (n = 2) of the control group, and 14.7% (n = 5) of the experimental group. The difference was statistically significant (p-value = 0.04). In the study by Benitz et al, the incidence of hypertension was also significantly higher in the fathers of the women with PCOS than it was in the control group (9.3% vs. 18.7%), (p-value < 0.05).[13]

Research limitations

Mental and physical tension, as well as the dietary habits of people, have an effect on the incidence of metabolic syndrome. Despite using the random sampling method, this aspect of the study was out of the researchers' control. Another limitation was its small sample size. Thus, it is recommended that further studies are conducted using larger populations.

Conclusion

Metabolic syndrome is a constellation of cardiometabolic risk factors, including insulin resistance, hyperglycaemia, dyslipidaemia, hypertension and myocardial infarction.[45-49] According to the results of this study, the families (fathers) of patients with PCOS consititute a high-risk group and should be screened regularly. As well as the patients suffering from PCOS, the first-degree relatives should also be evaluated for components of metabolic syndrome.

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