ORIGINAL ARTICLE

Insulin Resistance in First-Degree Relatives of the Patients with Polycystic Ovarian Syndrome

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Abstract

Objective: Insulin resistance and hyperinsulinemia are common among the women with polycystic ovarian syndrome (PCOS). Familial aggregation of PCOS has implications on the role of heredity in this disease. The aim of this study was to evaluate insulin resistance among the fathers, mothers, and siblings of the women with PCOS referring to the clinics affiliated to Shiraz University of Medical Sciences.

Materials and Methods: The present case-control study was conducted on 107 individuals as the case group and 107 individuals as the control group. After recording their height and weight, blood samples were obtained from all the participants in order to assay their serum insulin and blood sugar. Then, the participants were supposed to drink 75 gr glucose solutions and after lapsing 2 hours, blood samples were again taken from all the participants. Finally, the data were analyzed using independent t-test, Fisher's exact test, and chi-square test. *P*-values less than 0.05 were considered as statically significant. All the statistical analyses were performed through the SPSS statistical software (ver. 11.5).

Results: A significant difference was found between the two groups regarding glucose intolerance, obesity, and insulin resistance according to Homeostasis Model Assessment Index (HOMA) and Quantitative Insulin Sensitivity Check Index (QUICKI), and fasting insulin indexes (*P*<0.05). Moreover, a significant association was observed between android obesity and glucose intolerance (*P*<0.05), body mass index ($\geq$ 30 Kg/m^2), and type II diabetes in the two groups.

Conclusion: The first-degree relatives of the women suffering from polycystic ovarian syndrome constitute a risk group and early identification of insulin resistance may prevent the onset and progression of the disease.

Keywords: Insulin resistance, Impaired glucose tolerance, Polycystic ovarian syndrome

Introduction

Polycystic ovarian syndrome (PCOS) is the most common hyperandrogenic disorder in the women of reproductive age (1). In general, 5-10% of the women in reproductive age (15-45 years old) suffer from this disorder (1,2). This syndrome affects the

physiology and metabolism of body and eventually leads to detectable complications, including dyslipidemia, metabolic syndrome, obesity, and hypertension, as well as long-term consequences, such as type II diabetes (2), cardiovascular diseases, and endometrial cancer (3).

Nowadays, insulin resistance is considered as one of the most important risk factors for diabetes mellitus type II. Approximately 50-70% of the women with PCOS and 8-100% of the patients with type II diabetes have varying degrees of insulin resistance (4,6). Insulin resistance may be the result of obesity and is associated with hyperandrogenism (7).

Moreover, familial clustering of PCOS consistent with a genetic susceptibility to the disorder has been well documented (8,9).

In some studies, the incidence of premature baldness in men has been found in the first-degree relatives of the women with PCOS (3). However, these results were not confirmed by further studies (3,10). In the study conducted by Norman et al. (1996) on the parents of the patients with PCOS in Australia, hyperinsulinemia and elevated total cholesterol were respectively detected in 69% and 56% of the subjects, which was significantly higher compared to the control group ($P<0.05$). Thus, they suggested that the parents of the PCOS patients were at risk for cardiovascular diseases as well as diabetes (5). Furthermore, Yilmaz et al. conducted a study and showed that in comparison to the control group, the first-degree relatives of the PCOS patients had significantly higher serum fasting insulin, HOMA-IR and Log HOMA in all the subgroups (11).

To date, PCOS is highly prevalent and insulin resistance has been assumed to exist among the first-degree relatives of such patients. However, no studies have been conducted on this issue in Iran. Therefore, the present study aims to investigate insulin resistance and type II diabetes in the first-degree relatives of the PCOS women attending clinics in Shiraz.

Materials and Methods
Sampling of groups
This case-control study was conducted in Shiraz University of Medical Sciences in 2009. First, the PCOS patients whose disorder had been confirmed by clinical and paraclinical methods were identified. Then, their first-degree relatives (father, mother and siblings) who were over 30 years old and had the inclusion criteria of the study were interviewed as the case group. Afterwards, the first part of a questionnaire including demographic information was completed. In case the patients met all the inclusion criteria of the study and signed the written informed consents, they were entered into the study as the case group.

The control group consisted of the first-degree relatives of the women with no family history of PCOS. In order to ensure that these women had no history of PCOS, a complete history regarding regular menstrual periods and lack of hirsutism and infertility was taken and those having all the inclusion criteria were selected as the control group. The inclusion criteria of the study were not smoking, having no history of PCOS, being over 30 years old, and not using drugs affecting blood pressure and blood androgens.

Measurements & inclusion criteria
The case group included 107 patients (17 brothers, 34 fathers, 17 sisters, and 39 mothers). Also, 107 patients were enrolled into the control group. Then, body mass index (BMI) and waist-to-hip index were measured in the both groups. Before the blood test, the study participants were required not to use the drugs affecting blood pressure and androgens (the night and the morning before the tests) and have digestible dinner 10-12 hours before the test (i.e., abstinence from having solid and liquid food, except for water). Written informed consents for taking part in the study were also obtained from all the participants. All the subjects in the case group were first-degree relatives of the patients with PCOS as diagnosed by a physician. The diagnosis of

PCOS was based on history, clinical examination, laboratory tests, and ultrasound as well as tracking other diseases such as neoplasm, hyperprolactinemia, and congenital adrenal hyperplasia. Other inclusion criteria of the case group were being over 30 years old, not having a history of smoking, not having used drugs effecting blood sugar, blood pressure, cholesterol, and blood testosterone three months prior to the test, and having no history of PCOS.

Laboratory data

Blood samples were taken from all the participants between 7 and 9 A.M. and centrifuged for 30-45 minutes according to the standard protocols. For oral glucose tolerance test, 82.5 g glucose monohydrate dissolved in water was orally administered to the patients. Fasting blood glucose and fasting insulin levels were also measured in all the subjects. Moreover, serum was used for measurement of insulin. However, since insulin is only stable at -8 °C for 2 to 24 hours, a freezer with a temperature of -70°C was used for its long-term storage. After collecting all the samples, insulin was measured through the radioimmunoassay method using Mercodia kit (Sweden). Based on the above-mentioned kit, the natural insulin level was 2-25 MIU/L. Testosterone and fasting blood sugar were measured by the calorimetrically enzymatic method using Pars test kits (Tehran, Iran). Furthermore, fasting blood glucose, two hour blood sugar (OGTT), and Impaired Glucose Tolerance (IGT) were assessed according to the 1998 WHO criteria (12,13).

In this study, HOMA and QUICKI indexes were used for assessment of insulin resistance (7,14-17). HOMA index has been widely employed in the clinical research in order to assess the insulin sensitivity. This index is computed by multiplying the fasting blood sugar (mmol/L) by fasting insulin (μU/mL) divided by a constant as follows (18):

HOMA = fasting insulin (μU/ml) × fasting glycemia (mmol/L) / 22.5

Moreover, QUICKI index can be applied for normoglycaemic and hyperglycaemic patients.

It is calculated based on the inverse of the sum of the logarithmically expressed values of fasting glucose and insulin divided by a constant as follows (19,20):

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

In the current study, the subjects with HOMA≥2.38, QUICKI≤0.33, or fasting insulin (μU/ml) ≥10.58 were considered as insulin resistant (7,21,22). After performing the tests, the insulin resistant subjects were referred to an endocrinologist for further investigations.

Finally, the collected data were analyzed using the Statistical Package for the Social Sciences (SPSS 16) and Chi-square statistical test. P-values less than 0.05 were considered as statistically significant.

Results

According to HOMA index, the highest rate of insulin resistance was observed among the fathers of the case group (14.7%). Overall, 11.21% of the subjects in the case group and 3.74% of those in the control group showed insulin resistance, but the difference was not statistically significant (*P*=0.3).

On the other hand, based on the QUICKI index, insulin resistance was found in 14.01% of the case group subjects and 6.54% of the control group participants (*P*=0.2). In addition, the highest and lowest rates of insulin resistance were observed in the fathers of the case group (20.6%) and the brothers and sisters of the control group (5.9%), respectively.

Based on fasting insulin, 9.34% of the subjects in the case group and 1.87% of those in the control group showed insulin resistance (*P*=0.3). Moreover, the highest rate of insulin resistance was found among the fathers of the case group (11.76%).

Chi-square test revealed a significant relationship between insulin resistance based on HOMA, QUICKI, and fasting insulin indexes and android obesity (*P*<0.05) (Tables 1-3). In addition, a significant relationship was found between insulin resistance based on

HOMA and QUICKI indexes and obesity (BMI$\geq$30 kg/m^2) (*P*<0.05) (Tables 4,5).
Moreover, a statistically significant relationship was observed between insulin resistance based on fasting insulin and obesity in the case group, but not in the control group (Table 6).

Discussion
The present study showed that insulin resistance was accompanied by higher blood insulin levels to keep the blood glucose level within the normal range. According to the study results, insulin levels had increased in the case group compared to the control group; however, the difference was not statistically significant.
Elevated androgen levels (HA) lead to an increase in insulin levels and a decrease in glucose/insulin ratio which is suggestive of insulin resistance (23). Insulin resistance

affects the cellular signaling pathways and shows its negative effects in this way (24). Increased blood insulin directly affects the endothelial cells and increases the free acid blood levels, which relax the arterial wall that subsequently impairs the reduction of nitrogen oxide in the vascular wall (25). Moreover, increased blood levels of coagulation factors (factor VII, VIII) and anti-clotting factors lead to thrombotic status. As a result, the individuals with insulin resistance and metabolic syndrome can also be prone to the risk of vascular thrombosis (26).

In the present study, the prevalence of insulin resistance was higher among the relatives of the women with PCOS compared to the control group, but the difference was not statistically significant (*P*$\geq$0.05). Overall, 50-70% of the patients with PCOS have insulin resistance (23,27).

Table 1. Frequency distribution of insulin resistance according to HOMA index based on waist-to-hip ratio.

Groups		Case(n=107)*		Control(n=107)**	
Insulin-Resistant	**I.R**	**Without IR**	**I.R**	**Without IR**	
Android Obesity	Number (%)	Number (%)	Number (%)	Number (%)	
With AO[***]	11 (10.28)	21 (19.62)	4 (3.73)	20 (18.69)	
Without AO	1 (0.93)	74 (69.15)	0 (0)	83 (77.57)	
Total	12 (11.21)	95 (88.59)	4 (3.73)	103 (96.26)	

*: X2=12.7 df=1 *P*=0.001, **: X2=10.1 df=1 *P*=0.001, AO[***]: Android obesity, IR: Insulin-Resistant

Table 2. Frequency distribution of insulin resistance according to QUICKI index based on waist-to-hip ratio.

Groups		Case (n=107)		Control (n=107)	
Insulin Resistant	**IR**	**Without IR**	**IR**	**Without IR**	
Android Obesity	Number (%)	Number (%)	Number (%)	Number (%)	
With AO***	14 (13.08)	18 (16.82)	6 (6.54)	18 (16.82)	
Without AO	1 (0.93)	74 (69.15)	1 (0.93)	82 (76.63)	
Total	15 (14.01)	92 (22.97)	7 (7.47)	100 (93.45)	

*: X^2=21.47 df=1 *P*=0.001, **: X^2=24.56 df=1 *P*=0.00, AO[***]: Android obesity, IR: Insulin-Resistant

Table 3. Frequency distribution of insulin resistance according to fasting insulin index based on waist-to-hip ratio

Groups		Case(n=107)		Control(n=107)	
Insulin-Resistant	**I.R**	**Without IR**	**I.R**	**Without IR**	
Android Obesity	Number (%)	Number (%)	Number (%)	Number (%)	
With AO[***]	10 (9.35)	22 (20.5)	2 (1.87)	22 (20.5)	
Without AO	0 (0)	75 (70.09)	0 (0)	83 (77.57)	
Total	10 (9.35)	97 (90.65)	2 (1.87)	105 (98.1)	

*: X^2=6.62 df=1 *P*=0.001, **: X^2=6.68 df=1 *P*=0.001, AO[***]: Android obesity, IR: Insulin-Resistant

One study was conducted in Turkey in 2005 in order to evaluate insulin resistance and glucose intolerance among the first-degree relatives of the women with PCOS. The study results showed that 40% of the mothers and 52% of the fathers in the case group in comparison to 15% of the subjects in the control group had impaired glucose tolerance. Thus, it was concluded that not only the patients but also their first-degree relatives had the risk factors of cardiovascular diseases (4).

Furthermore, Sir-Petermann and colleagues performed a research in 2002 to assess glucose tolerance and insulin resistance in PCOS patients. In that study, 200 parents of PCOS patients were compared to the parents of healthy women and the results showed that the prevalence of type II diabetes was 1.89 times higher among the PCOS patients' parents compared to the control group. Also, insulin resistance was significantly higher among the PCOS patients' parents in comparison to the control group (28).

In another investigation, 23 brothers of the women with PCOS and 19 brothers of healthy women were studied. Secretion and insulin sensitivity were significantly higher in the case group compared to the control group. It was also reported that the PCOS women's brothers had the evidence of pancreas β cells impairment and would be at risk for type II diabetes. In the study by Sam, the brothers of the women with PCOS had dyslipidemia which is considered as a sign of insulin resistance (29).

Another study showed that insulin resistance, hyperandrogenism, and dehyroepiandrosterone sulfate (DHEAS) levels were higher among the female first-degree relatives of the women with PCOS compared to those of the healthy subjects (30).

In the present study, no significant insulin resistance was detected in the two study groups, which might be due to the small sample size of the study.

In our study, a significant relationship was observed between obesity as well as android obesity and insulin resistance based on

Table 4. Frequency distribution of insulin resistance according to HOMA index based on obesity (BMI≥30 kg/m²)

Groups	Case(n=107)		Control(n=107)	
Insulin-Resistant	**I.R**	**Without IR**	**I.R**	**Without IR**
Android obesity	Number (%)	Number (%)	Number (%)	Number (%)
With AO***	12 (11.21)	37 (34.57)	4 (3.73)	35 (32.7)
Without AO	0 (0)	58 (54.2)	0 (0)	68 (63.5)
Total	12 (11.21)	95 (59.58)	4 (3.73)	103 (96.26)

*: X^2=15.07 df=1 P=0.001, **: X^2=4.9 df=1 P=0.03, AO***: Android obesity, IR: Insulin-Resistant

Table 5. Frequency distribution of insulin resistance according to QUICKI index based on obesity (BMI≥30 kg/m²)

Groups	Case(n=107)		Control(n=107)	
Insulin-Resistant	**I.R**	**Without IR**	**I.R**	**Without IR**
Android obesity	Number (%)	Number (%)	Number (%)	Number (%)
BMI≥30kg/m²	14 (13.08)	35 (32.7)	6 (5.6)	33 (30.8)
BMI<30kg/m²	1 (0.93)	57 (53.27)	1 (0.93)	67 (93.6)
Total	15 (14.01)	92 (85.98)	7 (6.54)	100 (93.4)

*: X^2=24.84 df=1 P=0.001, **: X^2=12.05 df=1 P=0.001, AO***: Android obesity, IR: Insulin-Resistant

Table 6. Frequency distribution of insulin resistance according to fasting insulin index based on obesity (BMI≥30 kg/m²).

Groups	Case(n=107)		Control(n=107)	
Insulin-Resistant	**I.R**	**Without IR**	**I.R**	**Without IR**
Android obesity	Number (%)	Number (%)	Number (%)	Number (%)
BMI≥30kg/m²	10 (9.34)	39 (44.36)	2 (1.87)	37 (34.5)
BMI<30kg/m²	0 (0)	58 (54.2)	0 (0)	68 (63.5)
Total	10 (9.34)	97 (90.65)	2 (1.87)	105 (98.13)

*: X^2=10.62 df=1 P=0.001, **: X^2=3.28 df=1 P=0.007, AO***: Android obesity, IR: Insulin-Resistant

HOMA, QUICKI, and fasting insulin indexes in the two groups. The mechanisms linking obesity to the clinical manifestations of PCOS have not been completely understood. Nonetheless, obesity has a major impact on the severity of hyperandrogenism and insulin resistance (31). Insulin resistance is exacerbated in the obese women with PCOS (32-34). Many studies have also shown that insulin resistance decreases with weight loss (35,36).

Moreover, studies have shown that with the increase in BMI, insulin resistance increases as well (37). The strong relationship between obesity and type II diabetes can be explained by the predisposing genetic as well as environmental factors of obesity and insulin resistance (38). According to Hekimsoy et al. study, obesity is considered as an important risk factor for diabetes type II, hypertension, and hyperlipidemia. However, various results have been obtained in different studies regarding the relationship between the duration of obesity and these risks (39).

Up to now, various risk factors, such as PCOS, have been proposed for type II diabetes (40,41). Obesity, familial history of diabetes, and insulin resistance has also been mentioned as the risk factors of type II diabetes (42).

Studies show that Insulin resistance is an intrinsic defect of women with PCOS, and a high BMI could exacerbate insulin resistance in all women (43).

Overall, considering the higher insulin resistance in case group compared to the control group in the present study and other studies conducted on the issue, blood sugar screening, change in lifestyle, and weight control should be considered both in the PCOS patients and their families.

Conclusion

According to the findings of the present study, insulin resistance based on HOMA, QUICKI, and fasting insulin was significantly higher in the case group in comparison to the control group. Since insulin resistance can predispose to cardiovascular diseases and genetic factors play a key role in the incidence of insulin resistance, by screening the families of the patients suffering from insulin resistance, major steps can be taken toward primary and secondary prevention of high-risk disorders.

Acknowledgement

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