ORIGINAL PAPERS

Adv Clin Exp Med 2011, **20**, 2, 165–175
ISSN 1230-025X
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Metabolic Abnormalities in Siblings of Women with Polycystic Ovary Syndrome*

Zaburzenia metaboliczne u rodzeństwa kobiet z zespołem wielotorbielowatych jajników

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Abstract

Background. There is evidence of familial occurrence of metabolic disturbances in first-degree relatives of women with Polycystic Ovary Syndrome (PCOS).
Objectives. The aim of this study was to establish whether siblings of women with PCOS have the metabolic abnormalities that are typical of PCOS.
Material and Methods. Forty-four sisters and forty-two brothers of women with PCOS were recruited. There were two control groups consisting of 70 healthy women and 30 healthy men. Anthropometric and metabolic parameters (glucose and insulin, fasting and during an oral glucose tolerance test (OGTT 30', 60' and 120'), insulin-sensitivity and insulin-resistance indexes, lipidogram) were assessed in all subjects.
Results. In comparison with the controls, siblings of women with PCOS had higher glucose levels, higher insulin levels at 120' and higher mean insulin levels during the OGTT. There were no differences in the insulin-sensitivity indexes or insulin resistance indexes between siblings and the controls. The total cholesterol and LDL-cholesterol levels were higher in sisters and brothers of women with PCOS than in the controls.
Conclusions. Siblings of patients with PCOS are predisposed to some metabolic abnormalities, such as higher fasting glycemia, glucose intolerance and a more adverse lipid profile than the controls. Insulin resistance in PCOS families is related mainly to obesity and seems not to have a genetic background (**Adv Clin Exp Med 2011, 20, 2, 165–175**).

Key words: PCOS, siblings, familial occurrence, metabolic disturbances.

Streszczenie

Wprowadzenie. Istnieją dane na temat rodzinnego występowania zaburzeń metabolicznych u krewnych pierwszego stopnia kobiet z zespołem wielotorbielowatych jajników (PCOS).
Cel pracy. Ocena rodzeństwa kobiet z PCOS pod kątem występowania zaburzeń metabolicznych.
Materiał i metody. Zbadano 44 siostry i 42 braci pacjentek z PCOS. Grupy kontrolne stanowiło 70 zdrowych kobiet i 30 zdrowych mężczyzn. U wszystkich zrekrutowanych oceniono wskaźniki antropometryczne i metaboliczne (stężenia glukozy i insuliny na czczo oraz podczas doustnego testu obciążenia glukozą – OGTT – 30', 60' i 120', wskaźniki insulinowrażliwości i insulinooporności oraz pełny lipidogram).
Wyniki. Rodzeństwo kobiet z PCOS w porównaniu z odpowiednimi grupami kontrolnymi miało większe stężenia glukozy podczas OGTT oraz stężenia insuliny w 120' i średnie stężenia insuliny podczas OGTT. Nie było różnic dotyczących wartości wskaźników insulinowrażliwości i insulinooporności między rodzeństwem pacjentek z PCOS a odpowiednimi grupami kontrolnymi. Siostry i bracia charakteryzowali się większymi stężeniami cholesterolu całkowitego i cholesterolu LDL niż osoby z grup kontrolnych.
Wnioski. Rodzeństwo pacjentek z PCOS jest predysponowane do występowania zaburzeń metabolicznych, takich jak: nieprawidłowa tolerancja glukozy, większe stężenia glukozy na czczo oraz bardziej niekorzystny profil lipidowy w porównaniu z rodzeństwem zdrowych kobiet. Insulinooporność w rodzinach pacjentek z PCOS jest związana z otyłością i wydaje się, że nie ma podłoża genetycznego (**Adv Clin Exp Med 2011, 20, 2, 165–175**).

Słowa kluczowe: PCOS, rodzeństwo, występowanie rodzinne, zaburzenia metaboliczne.

* The work was supported by University Grant number 1636.

Polycystic ovary syndrome (PCOS) is among the most commonly diagnosed endocrinopathies in women of reproductive age. The symptoms of PCOS include the consequences of androgen excess, chronic anovulation and infertility. Patients with PCOS are also at increased risk for obesity, insulin resistance, dyslipidemia, metabolic syndrome, glucose intolerance and diabetes mellitus [1–5]. Familial aggregation of PCOS is well documented and suggests a genetic susceptibility to the disorder. Family studies of PCOS have investigated not only the occurrence of hormonal abnormalities, but also metabolic abnormalities among the first-degree relatives of women with PCOS. It has been observed that both female and male relatives may have metabolic disturbances similar to those found in patients with PCOS, such as insulin resistance and dyslipidemia [6–12].

The aim of the present study was to determine whether brothers and sisters of patients with PCOS differ from healthy siblings of healthy women in terms of metabolic parameters.

Material and Methods

The study included 44 sisters and 42 brothers of women diagnosed with PCOS (according to the Rotterdam criteria) who were patients of the Department of Endocrinology, Diabetology and Isotope Treatment of Wroclaw Medical University. The control groups consisted of 70 healthy women and 30 healthy men whose sisters did not have PCOS, menstrual disturbances or hirsutism. The study groups were divided into two subgroups according to body mass index (BMI): those with BMI < 25 kg/m^2 and those with BMI ≥ 25 kg/m^2.

None of the participants in the study had previously been treated with hormonal or insulin-sensitizing drugs, and they all stated that during the three months prior to the study they had not been on any special diet or practiced intense physical exercise, that they had consumed alcohol only occasionally, and that they had not smoked more than five cigarettes a day. Persons with hypercortisolemia, hyperprolactinemia, impaired thyroid function, or suspicion of ovarian or adrenal tumor were excluded from the study.

The study protocol was approved by the Ethics Committee of Wroclaw Medical University, and all the subjects gave their informed consent in writing.

A physical examination of all the subjects was carried out, including anthropometrical measurements: body mass, body height, and waist and hip circumference. The body mass index was calculated using the equation: body mass [kg]/height-squared [m^2]. The waist-to-hip ratio (WHR) was calculated using the equation: waist circumference [cm]/hip circumference [cm].

Blood for laboratory tests was collected between 8:00 and 10:00 AM after overnight fasting, at least eight hours after the last meal. An oral glucose tolerance test (OGTT) was performed for all subjects; blood for measuring glucose and insulin was collected after 0, 30, 60 and 120 minutes.

Serum concentrations of glucose, total cholesterol (TC), HDL cholesterol, and triglycerides were measured by routine enzymatic methods (Dade Behring Marburg GmbH, Germany) and LDL-cholesterol was calculated from Friedewald's formula: LDL-cholesterol [mg/dl] = total cholesterol [mg/dl] – HDL-cholesterol [mg/dl] – (triglycerides [mg/dl]/5). Serum insulin concentrations were determined by a chemifluorescent method using an Immulite 2000 analyzer (DPC, Diagnostic Products Corporation, Los Angeles, USA).

To estimate insulin sensitivity, insulin-sensitivity indexes and insulin-resistance indexes were computed as shown below, where I_0 is fasting insulin, G_0 is fasting glucose, I_{mean} is the mean insulin concentration during OGTT and G_{mean} is the mean glucose concentration during OGTT):

– HOMA – insulin-resistance index: (I_0 (μIU/ml) × G_0 (mmol/l))/22.5 [13],

– FIRI – insulin-resistance index: (I_0 (μIU /ml) × G_0 (mmol/l))/25 [14],

– QUICKI – insulin-sensitivity index: 1/[log I_0 (μIU/ml) + log G_0 (mg/dl)] [15],

– insulin-sensitivity index of Matsuda and DeFronzo, the MATSUDA index: $10000/\sqrt{[(G_0 \text{ (mg/dl)} \times G_{mean} \text{ (mg/dl)}) \times (I_0 \text{ (μIU/ml)} \times I_{mean} \text{ (μIU/ml)})]}$ [16].

Statistical Analysis

The Shapiro-Wilk test assessing the normality of the data distribution was used to evaluate the assumptions of the parametric tests. To assess the differences between groups, the data were analyzed by means of the Student's *t* test. In the absence of a normal distribution, the non-parametric Mann-Whitney *U* test was used. The variability of the tested features due to the group and body mass index was studied using a two-factorial analysis of variance. A post-hoc comparison between the groups was made with Tukey's LSD test. The level of statistical significance was set at $p < 0.05$.

Results

Neither the main groups of women (S_{PCOS}, $CG_{♀}$) nor the main groups of men (B_{PCOS}, $CG_{♂}$)

differed significantly in terms of average age and average values of the anthropometric parameters (Tables 1 and 2).

The parameters of carbohydrate metabolism (glucose and insulin during the OGTT) in the sisters of patients with PCOS and the women in the control group are summarized in Table 3. A significantly higher mean fasting glucose concentration was noted in the sisters than in the women in the control group. The sisters of patients with PCOS had a significantly higher mean concentration of insulin at 120' of the OGTT than the women in the control group. Both the subgroups of sisters of PCOS patients (those with BMI ≥ 25 and those with BMI < 25) showed a significantly higher mean concentration of insulin at 120' of the OGTT and a higher mean concentration of insulin during the OGTT than the corresponding subgroups of control-group women.

The mean values of the insulin-resistance and insulin-sensitivity indexes in the sisters of patients with PCOS and in the control group of women are shown in Table 4. In the subgroup of sisters with BMI <25, a significantly lower mean value of the

Table 1. Comparison of age, BMI and WHR in the sisters of patients with PCOS and the control group of women
Tabela 1. Porównanie wieku oraz wskaźników BMI i WHR u sióstr pacjentek z PCOS oraz kobiet z grupy kontrolnej

		S_{PCOS}	$CG_{♀}$	p
Age – years (Wiek – lata)	whole group	25.523 ± 5.781	24.90 ± 4.250	ns.
	BMI ≥ 25	27.571 ± 4.183	26.571 ± 5.186	ns.
	BMI < 25	24.567 ± 6.224	23.228 ± 2.001	ns.
BMI kg/m²	whole group	24.220 ± 6.085	25.712 ± 6.271	ns.
	BMI ≥ 25	30.579 ± 6.741	30.596 ± 5.296	ns.
	BMI < 25	21.253 ± 2.428	20.827 ± 1.628	ns.
WHR	whole group	0.794 ± 0.053	0.807 ± 0.062	ns.
	BMI ≥ 25	0.808 ± 0.044	0.840 ± 0.058	ns.
	BMI < 25	0.787 ± 0.056	0.774 ± 0.046	ns.

S_{PCOS} – sisters of patients with PCOS.
$CG_{♀}$ – women of control group.

S_{PCOS} – siostry pacjentek z PCOS.
$CG_{♀}$ – kobiety w grupie kontrolnej.

Table 2. Comparison of age, BMI and WHR in the brothers of patients with PCOS and the control group of men

Tabela 2. Porównanie wieku oraz wskaźników BMI i WHR u braci pacjentek z PCOS oraz mężczyzn z grupy kontrolnej

		B_{PCOS}	$CG_{♂}$	p
Age – years (Wiek – lata)	whole group	23.524 ± 5.052	24.10 ± 1.749	ns.
	BMI ≥ 25	26.60 ± 4.309	25.10 ± 2.025	ns.
	BMI < 25	20.727 ± 3.978	23.60 ± 1.392	ns.
BMI kg/m²	whole group	24.443 ± 4.003	24.868 ± 3.767	ns.
	BMI ≥ 25	27.673 ± 3.086	29.340 ± 2.634	ns.
	BMI < 25	21.506 ± 1.919	22.631 ± 1.605	0.075
WHR	whole group	0.892 ± 0.069	0.878 ± 0.062	ns.
	BMI ≥ 25	0.940 ± 0.061	0.933 ± 0.064	ns.
	BMI < 25	0.853 ± 0.047	0.850 ± 0.039	ns.

B_{PCOS} – brothers of patients with PCOS
$CG_{♂}$ – men of control group.

S_{PCOS} – bracia pacjentek z PCOS.
$CG_{♂}$ – mężczyźni w grupie kontrolnej.

Table 3. Comparison of concentrations of glucose and insulin during the OGTT in the sisters of patients with PCOS and the control group of women

Tabela 3. Porównanie stężeń glukozy i insuliny podczas OGTT u sióstr pacjentek z PCOS oraz kobiet z grupy kontrolnej

		S_{PCOS}	$CG_{♀}$	p
Glucose 0' (Glukoza 0') mg/dl	whole group	87.227 ± 7.139	81.686 ± 8.321	< 0.001
	BMI ≥ 25	92.0 ± 7.716*	85.343 ± 7.507	0.01616
	BMI < 25	85.0 ± 5.723*	78.028 ± 7.524	< 0.001
Glucose 120' (Glukoza 120') mg/dl	whole group	87.232 ± 26.047	83.071 ± 19.501	ns.
	BMI ≥ 25	102.0 ± 20.408*	87.514 ± 21.270	0.02473
	BMI < 25	80.833 ± 25.887*	78.628 ± 16.695	ns.
Glucose mean (Glukoza średnia) mg/dl	whole group	101.669 ± 18.100	96.243 ± 15.280	0.09061
	BMI ≥ 25	108.596 ± 15.311	101.914 ± 15.354	ns.
	BMI < 25	98.667 ± 18.618	90.571 ± 13.112	0.03401
Insulin 0' (Insulina 0') µIU/ml	whole group	7.793 ± 5.375	8.964 ± 7.335	ns.
	BMI ≥ 25	12.092 ± 7.050*	11.559 ± 8.599	ns.
	BMI < 25	5.930 ± 3.066*	6.443 ± 4.748	ns.
Insulin 120' (Insulina 120') µIU/ml	whole group	37.579 ± 23.815	27.662 ± 36.667	< 0.001
	BMI ≥ 25	53.938 ± 30.917*	36.850 ± 48.931	0.00131
	BMI < 25	30.490 ± 15.935*	18.737 ± 14.097	0.00115
Insulin mean (Insulin średnia) µIU/ml	whole group	36.744 ± 19.091	33.534 ± 26.637	0.05829
	BMI ≥ 25	48.452 ± 16.003*	42.407 ± 32.493	0.02860
	BMI < 25	31.671 ± 18.270*	24.915 ± 15.464	0.03456

* Statistically significant difference between the subgroup of sisters of PCOS patients with BMI ≥ 25 and BMI < 25.

* Statystycznie istotna różnica między podgrupą sióstr pacjentek z PCOS i BMI ≥ 25 a BMI < 25.

MATSUDA index than in the corresponding control group was observed.

The parameters of carbohydrate metabolism (glucose and insulin during the OGTT) of the brothers of patients with PCOS and the men in the control group are summarized in Table 5. The brothers had significantly higher mean fasting glucose and glucose levels during the OGTT than the men in the control group. The brothers with BMI < 25 had a significantly higher mean fasting glucose concentration and mean concentration of glucose during the OGTT than corresponding subgroup among the control-group men.

The brothers of patients with PCOS had significantly higher concentrations of insulin during the OGTT than the control-group men. There were no significant differences between these groups in terms of insulin-resistance and insulin-sensitivity indexes (Table 6).

The average concentrations of total cholesterol and LDL-cholesterol were significantly higher among the sisters of PCOS patients than in the control-group women. The differences in lipid parameters between the subgroups of sisters with BMI < 25 and their controls were similar (Table 7).

The average concentrations of total cholesterol and LDL-cholesterol were significantly higher in the group of brothers of patients with PCOS than in the control-group men. The differences between the lipid parameters of the subgroup of brothers with BMI ≥ 25 and the relevant control group were similar to the differences between the main groups' lipid parameters (Table 8).

Table 4. Comparison of values of insulin-resistance and insulin-sensitivity indexes in the sisters of PCOS patients and the control group of women

Tabela 4. Porównanie wartości wskaźników insulinooporności i insulinowrażliwości u sióstr pacjentek z PCOS oraz kobiet z grupy kontrolnej

		S_{PCOS}	$CG_{♀}$	p
HOMA	whole group	1.709 ± 1.270	1.856 ± 1.713	ns.
	BMI ≥ 25	2.755 ± 1.679*	2.488 ± 2.085	ns.
	BMI < 25	1.255 ± 0.682*	1.242 ± 0.929	ns.
FIRI	whole group	1.538 ± 1.143	1.670 ± 1.542	ns.
	BMI ≥ 25	2.480 ± 1.511*	2.239 ± 1.876	ns.
	BMI < 25	1.130 ± 0.613*	1.118 ± 0.836	ns.
QUICKI	whole group	0.367 ± 0.035	0.370 ± 0.047	ns.
	BMI ≥ 25	0.339 ± 0.032*	0.352 ± 0.043	ns.
	BMI < 25	0.379 ± 0.029*	0.389 ± 0.043	ns.
MATSUDA	whole group	8.417 ± 4.141	10.272 ± 6.876	ns.
	BMI ≥ 25	5.111 ± 2.308*	7.263 ± 4.214	0.05103
	BMI < 25	9.850 ± 3.951*	13.195 ± 7.712	0.03078

* Statistically significant difference between the subgroups of sisters of PCOS patients with BMI ≥ 25 and BMI < 25.

* Statystycznie istotna różnica między podgrupą sióstr pacjentek z PCOS i BMI ≥ 25 a BMI < 25.

Discussion

Metabolic disorders, such as impaired fasting glycemia, glucose intolerance, insulin resistance and atherogenic dyslipidemia, are common in patients with PCOS. Around 7.5% of obese women with PCOS have type 2 diabetes [2]. Recent reports indicate familial occurrence of these metabolic disorders, especially in first-degree relatives of women with PCOS [8, 10–12, 17].

The present study shows that sisters of patients with PCOS, regardless of BMI, had higher glucose concentrations than the women in the control group. Significant differences were found in fasting glucose concentrations. In three sisters (6.8%) impaired fasting glycemia was noted, and glucose intolerance in two others (4.5%). In the control group, only one woman (1.3%) had glucose intolerance. Overall, 11.4% of the sisters showed prediabetic status (impaired fasting glycemia or glucose intolerance), but none of the sisters were diagnosed with type 2 diabetes. Similar results were obtained by Yildiz et al., who observed impaired glucose tolerance in 5% of sisters of PCOS patients; however, no abnormal fasting glycemia was noted in these relatives [8]. The results of the current study are in accordance with a recently published report in which higher fasting glucose levels were noted among first-degree female relatives of patients with PCOS than in a control group of women. In addition, impaired glucose tolerance was diagnosed in 5.7% of these relatives [18].

In the current study, a trend towards increased insulin concentrations during the OGTT was noted among the sisters of patients with PCOS as compared with the control-group women. The exception was the fasting insulin concentration, which was slightly lower in the sisters than in the controls. The concentration of insulin during the OGTT, especially at 120 minutes, and the mean concentration of insulin during the OGTT, were higher in the sisters of PCOS patients than in the control-group women, regardless of BMI. The sisters were characterized by lower insulin-sensitivity index values than the respective control groups, but this difference was statistically significant only for the MATSUDA index in the subgroups with BMI < 25. Only fasting concentrations of glucose and insulin are used for the calculation of HOMA, FIRI, and QUICKI. In this study the sisters of PCOS patients did not show increased fasting insulin concentrations compared with the controls, but had a higher mean concentration of insulin. This may explain why no major differences were

Table 5. Comparison of concentrations of glucose and insulin during the OGTT in the brothers of patients with PCOS and the control group of men

Tabela 5. Porównanie stężeń glukozy i insuliny podczas OGTT u braci pacjentek z PCOS oraz mężczyzn z grupy kontrolnej

		B_{PCOS}	$CG_{♂}$	p
Glucose 0' (Glukoza 0') mg/dl	whole group	89.333 ± 6.083	85.933 ± 6.373	0.01540
	BMI ≥ 25	90.0 ± 5.534	87.20 ± 7.899	ns.
	BMI < 25	88.727 ± 6.613	85.30 ± 5.583	0.04967
Glucose 120' (Glukoza 120') mg/dl	whole group	84.976 ± 19.697	71.60 ± 22.841	0.00975
	BMI ≥ 25	84.250 ± 24.659	74.90 ± 28.614	ns.
	BMI < 25	85.636 ± 14.364	69.950 ± 19.996	0.00181
Glucose mean (Glukoza średnia) mg/dl	whole group	110.095 ± 15.440	95.575 ± 15.777	< 0.001
	BMI ≥ 25	113.275 ± 15.956	102.350 ± 21.270	0.05680
	BMI < 25	107.204 ± 14.721	92.187 ± 11.376	0.00120
Insulin 0' (Insulina 0') µIU/ml	whole group	7.393 ± 4.541	8.987 ± 4.883	ns.
	BMI ≥ 25	8.915 ± 5.288*	10.560 ± 4.498	ns.
	BMI < 25	6.001 ± 3.277*	8.20 ± 4.986	0.08357
Insulin 120' (Insulina 120') µIU/ml	whole group	25.812 ± 16.322	15.213 ± 12.418	0.00385
	BMI ≥ 25	26.455 ± 20.766	11.780 ± 6.610	0.03680
	BMI < 25	25.227 ± 11.367	16.930 ± 14.330	0.01056
Insulin mean (Insulina średnia) µIU/ml	whole group	38.268 ± 22.730	25.538 ± 12.262	0.00532
	BMI ≥ 25	42.172 ± 24.122	27.882 ± 8.024	ns.
	BMI < 25	34.718 ± 21.319	24.366 ± 13.952	0.02354

* Statistically significant difference between the subgroups of brothers of patients with PCOS with BMI ≥ 25 and BMI < 25.

* Statystycznie istotna różnica między podgrupą braci pacjentek z PCOS i BMI ≥ 25 a BMI < 25.

observed between the insulin-resistance indexes of the sisters of PCOS patients and those of the controls. It also shows why the MATSUDA index seems to be a better measure of insulin sensitivity. Fasting concentrations of glucose and insulin and their average concentrations from the OGTT are used to calculate the MATSUDA index. It is currently believed that the MATSUDA index correlates best with the values of the insulin-resistance indexes obtained using the euglycemic clamp technique [16].

The observations of many researchers show unambiguously that sisters of PCOS patients have elevated levels of insulin and insulin-resistance indexes [8, 11, 17–20]. Yildiz et al. demonstrated that sisters with BMI < 25 and with normal glucose tolerance had higher fasting insulin levels, increased areas under the curve for insulin concentration during the OGTT and higher HOMA indexes than an age- and BMI-matched control group of women [8]. Thus they demonstrated that, as in lean patients with PCOS, insulin resistance also occurs in their lean sisters. This suggests that there is a genetic predisposition for the development of insulin resistance in the families of PCOS women and that it is independent of obesity. The results of the present study show that overweight or obese sisters had significantly higher concentrations of fasting insulin and insulin during the OGTT, higher insulin-resistance index values and lower insulin-sensitivity index rates than lean sisters, which suggests that obesity plays a significant role in the development of insulin resistance in sisters of patients with PCOS. Legro et al. described insulin resistance in sisters of women with PCOS who also had PCOS or hyperandrogenemia [11].

Table 6. Comparison of values of insulin-resistance and insulin-sensitivity indexes in the brothers of PCOS patients and the control group of men

Tabela 6. Porównanie wartości wskaźników insulinooporności i insulinowrażliwości u braci pacjentek z PCOS oraz mężczyzn z grupy kontrolnej

		B_{PCOS}	$CG_{♂}$	p
HOMA	whole group	1.627 ± 0.990	1.921 ± 1.102	ns.
	BMI ≥ 25	1.966 ± 1.145*	2.324 ± 1.131	ns.
	BMI < 25	1.320 ± 0.720*	1.720 ± 1.058	ns.
FIRI	whole group	1.465 ± 0.891	1.729 ± 0.992	ns.
	BMI ≥ 25	1.769 ± 1.030	2.091 ± 1.018	ns.
	BMI < 25	1.879 ± 0.648	1.548 ± 0.953	ns.
QUICKI	whole group	0.368 ± 0.036	0.357 ± 0.033	ns.
	BMI ≥ 25	0.357 ± 0.037	0.344 ± 0.027	ns.
	BMI < 25	0.377 ± 0.033	0.364 ± 0.0347	ns.
MATSUDA	whole group	8.173 ± 4.928	9.356 ± 4.759	ns.
	BMI ≥ 25	6.983 ± 3.980	7.026 ± 2.334	ns.
	BMI < 25	9.255 ± 5.524	10.521 ± 5.263	ns.

* Statistically significant difference between the subgroups of brothers of PCOS patients with BMI ≥ 25 and BMI < 25.

* Statystycznie istotna różnica między podgrupą braci pacjentek z PCOS i BMI ≥ 25 a BMI < 25.

Table 7. Comparison of lipid parameters in the sisters of patients with PCOS and the control group of women

Tabela 7. Porównanie wskaźników lipidogramu u sióstr pacjentek z PCOS oraz kobiet z grupy kontrolnej

		S_{PCOS}	$CG_{♀}$	p
TC mg/dl	whole group	189.454 ± 34.396	177.043 ± 34.371	0.01898
	BMI ≥ 25	196.143 ± 25.407	184.143 ± 38.462	0.08377
	BMI < 25	186.333 ± 37.857	169.943 ± 28.537	0.04298
LDL-C mg/dl	whole group	107.535 ± 30.416	95.811 ± 29.744	0.03985
	BMI ≥ 25	116.143 ± 19.887	104.559 ± 33.288	ns.
	BMI < 25	103.379 ± 33.899	87.314 ± 23.304	0.04472
HDL-C mg/dl	whole group	67.302 ± 16.650	63.271 ± 16.181	ns.
	BMI ≥ 25	60.357 ± 14.254	57.486 ± 16.218	ns.
	BMI < 25	70.655 ± 16.904	69.057 ± 14.121	ns.
TG mg/dl	whole group	75.50 ± 34.767	86.428 ± 60.193	ns.
	BMI ≥ 25	98.286 ± 42.203*	113.571 ± 74.096	ns.
	BMI < 25	64. 867 ± 25.024*	59.286 ± 18.597	ns.

* Statistically significant difference between the subgroups of sisters of PCOS patients with BMI ≥ 25 and BMI < 25.

* Statystycznie istotna różnica między podgrupą sióstr pacjentek z PCOS i BMI ≥ 25 a BMI < 25.

Table 8. Comparison of mean values of lipid parameters in the brothers of patients with PCOS and the control group

Tabela 8. Porównanie wskaźników lipidogramu u braci pacjentek z PCOS oraz mężczyzn z grupy kontrolnej

		B_{PCOS}	$CG_{♂}$	p
TC mg/dl	whole group	184.309 ± 40.220	161.167 ± 32.711	0.01050
	BMI ≥ 25	209.50 ± 37.099*	168.20 ± 37.297	0.00478
	BMI < 25	161.409 ± 27.554*	157.650 ± 30.581	ns.
LDL-C mg/dl	whole group	105.683 ± 39.882	88.533 ± 26.470	0.04451
	BMI ≥ 25	127.158 ± 44.344*	91.40 ± 31.081	0.01881
	BMI < 25	87.136 ± 23.803*	87.10 ± 24.604	ns.
HDL-C mg/dl	whole group	59.951 ± 14.807	57.733 ± 14.839	ns.
	BMI ≥ 25	58.947 ± 16.403	50.10 ± 10.650	ns.
	BMI < 25	60.818 ± 13.612	61.550 ± 15.374	ns.
TG mg/dl	whole group	91.714 ± 44.322	91.0 ± 59.808	ns.
	BMI ≥ 25	118.650 ± 39.125*	133.10 ± 83.842	ns.
	BMI < 25	67.227 ± 33.632*	70.10 ± 27.154	ns.

* Statistically significant difference between the subgroups of brothers of PCOS patients with BMI ≥ 25 and BMI < 25.

* Statystycznie istotna różnica między podgrupą braci pacjentek z PCOS i BMI ≥ 25 a BMI < 25.

Those authors suggested a relationship between hyperandrogenemia, impaired carbohydrate metabolism and insulin resistance in families of PCOS women, and inheritance of these anomalies in first-degree relatives of these women.

In addition to disorders of carbohydrate metabolism, lipid disorders have also been observed in sisters of PCOS patients. However, not all authors agree on this. Raskauskiene et al. [21] and Yilmaz et al. [17] found no differences between the lipid parameters of sisters of PCOS patients and those of control groups. In contrast, Sam et al. found significantly higher concentrations of total cholesterol, LDL-cholesterol and triglycerides in patients with PCOS sisters [12]. The concentration of LDL-cholesterol was significantly higher in the sisters with hyperandrogenemia than in the sisters without increased levels of androgens, and the concentrations of triglycerides were higher in sisters with PCOS than in other sisters. Sam concluded that, in both women with PCOS and their sisters, an increased concentration of LDL-cholesterol is associated with hyperandrogenemia, and hypertriglyceridemia is associated with insulin resistance. In the present study, as in that of Sam et al., higher concentrations of total cholesterol and LDL-cholesterol were observed in the sisters of PCOS patients than in the control-group women. These concentrations were higher in both subgroups of sisters, regardless of BMI. No differences in these parameters were seen between the lean sisters and the overweight or obese ones, while triglyceride concentrations were significantly higher in the group of sisters with BMI ≥ 25 than in the lean ones. Thus it appears that insulin resistance associated with obesity is a factor influencing triglyceride levels. Like some of the previously mentioned authors [17, 19], we did not find differences between the concentrations of HDL-cholesterol and triglycerides in the sisters of PCOS patients and in the control-group women.

In the current study, the brothers of patients with PCOS showed essentially similar metabolic disturbances as the sisters. Compared with the men in the control group, they were characterized by higher fasting glucose concentrations during the OGTT. No differences were noted in the concentrations of glucose between the lean brothers and the overweight or obese brothers. This may indicate that obesity is not a key factor influencing the concentration of glucose in brothers of patients with PCOS, but it may have a family background. Impaired fasting glycemia was identified in two of the brothers (4.8%), and one of them (2.4%) showed impaired glucose tolerance. In the control group, only one man had impaired fast-

ing glycemia (3.3%). These results are consistent with those of other authors. Yildiz et al. observed impaired fasting glycemia in 4% of the brothers of patients with PCOS [8]. Baillargeon et al. found glucose intolerance in 17.6% of the brothers of patients with PCOS – a much larger proportion than in this study [22]. Baillargeon et al. demonstrated that, compared with men matched in terms of age, BMI, waist circumference and body fat content, the brothers of patients with PCOS had significantly higher glucose concentrations at 120 minutes of the OGTT and increased areas under the curve, as well as higher fasting glucose concentrations. The concentration of glucose at 120 minutes of the OGTT as a screening test is more important than the information gained from the concentration of fasting glucose, because high basal concentrations of insulin are sufficient to keep glucose within the normal range when fasting, but are often insufficient for the satisfactory adjustment of the carbohydrate level after a glucose load [23, 24].

The brothers of PCOS patients, like the sisters, were characterized by higher concentrations of insulin in the OGTT than the control-group men. The exception was fasting insulin concentration, which was slightly lower in the group of brothers. Overweight and obesity had a significant effect on the insulin level. The fasting insulin concentration was significantly lower in the lean brothers than in the overweight or obese brothers. The obese or overweight brothers had lower levels of SHBG than the lean brothers (data not shown), and it is known that the concentration of SHBG depends on obesity status as well as the degree of insulin resistance [25]. Neither of the analyzed groups of brothers differed from the corresponding control groups of men in terms of insulin resistance or insulin sensitivity. This can be partly explained, as with the sisters, by the fact that the brothers did not differ from the control group in the concentration of fasting insulin, and even had slightly lower fasting insulin levels. We did not observe statistically significant differences in the MATSUDA index, although the brothers were characterized by slightly lower values. The overweight or obese brothers had higher values in the HOMA insulin-resistance index and lower insulin-sensitivity index values than the lean brothers, which once again points to the dominant role of obesity as an influence on insulin resistance among relatives of patients with PCOS.

Many authors have reported the presence of insulin resistance in brothers of patients with PCOS [17, 22, 26, 27]. Most of them used HOMA as an insulin resistance indicator. Assuming – in accordance with the criteria used by other authors [28, 29] – that a HOMA value > 2.5 indicates insulin resistance, in the current study insulin resistance was found in 19% of the brothers of PCOS patients. However, this percentage is comparable to the percentage of insulin resistance among the control-group men (20%). In both groups, insulin resistance was found mostly in men with BMI ≥ 25. Similar results were obtained by Yildiz et al. [8]. They did not observe differences in the parameters of insulin resistance between brothers of patients with PCOS and their control-group men, but they found that the former were characterized by a much higher value of the area under the curve for insulin during the OGTT. Yilmaz et al. [17] and Sam et al. [27], contrary to our results, demonstrated higher fasting insulin concentrations in male relatives of women with PCOS. Baillargeon et al., using the euglycemic clamp, found decreased insulin sensitivity in 38% of brothers of patients with PCOS [22].

In the present study, higher concentrations of insulin were observed during the OGTT among the siblings of women with PCOS. But contrary to results of other authors, fasting insulin levels were lower in those relatives. As shown by Colilla et al., women with PCOS and their relatives are predisposed to β-cell dysfunction and abnormal insulin secretion and action [30]. The degree of this dysfunction could reflect the severity of primary disorders of the basal and postprandial secretion of insulin in relatives of patients with PCOS. It is likely that genetic β-cell dysfunction results in relatively lower basal secretion of insulin, and so differences were not found between the fasting insulin levels of siblings of PCOS patients and the control groups.

Fasting hyperinsulinemia is present mainly in obese, not lean, PCOS women. Higher insulin levels after a glucose load are observed in lean as well as obese patients with PCOS [1]. It seems that primary genetic defect in PCOS families is related to insulin response to an oral glucose load, while the fasting insulin level depends mainly on obesity and environmental factors. Genetically determined abnormal β-cell function in women with PCOS and their relatives is a component of glucose intolerance, and is a risk factor for developing diabetes mellitus, independent of insulin resistance [30, 31]. So siblings of women with PCOS, although they do not show insulin resistance, but have metabolic disturbances related with β-cell dysfunction, such as abnormal glucose tolerance and higher insulin levels in the OGTT, are at risk for diabetes mellitus type 2.

In the brothers of patients with PCOS, as in their sisters, higher concentrations of total cholesterol and LDL-cholesterol were observed than in the controls, although these values were within the normal limits. There were statistically significant

differences concerning total cholesterol and LDL--cholesterol between the whole group of brothers and the whole male control group, and also between the subgroup of overweight or obese brothers and the respective control subgroup. Other authors also described adverse lipid profiles in brothers of PCOS patients compared with control-group men. In contrast to the results of the present study, they observed not only higher concentrations of total and LDL-cholesterol, but also of triglycerides in male relatives of patients with PCOS [17, 20, 22, 27]. There were no differences in HDL-cholesterol level between brothers and controls, either in the current study or in those mentioned above [17, 22].

In the current study, in contrast to the findings of most authors, siblings of women with PCOS did not demonstrate all the metabolic disturbances that are typical of PCOS. Higher glucose levels, glucose intolerance, higher insulin levels after glucose load and higher total and LDL-cholesterol levels were observed in siblings of PCOS patients. However, they did not reveal the disorders most typical of PCOS: insulin resistance and atherogenic dyslipidemia. This probably results from the fact that in PCOS these abnormalities do not have a genetic background. Insulin resistance and an atherogenic lipid profile are strongly related to obesity, among the siblings of women with PCOS and the controls as well.

Undoubtedly, siblings of women with PCOS are at greater risk for contracting type 2 diabetes and cardiovascular diseases than healthy counterparts in the general population, but this risk is not as large as for PCOS patients themselves. For these reasons the entire families of patients with PCOS should be included in the primary and secondary prevention of cardiovascular diseases and diabetes.

The authors concluded that siblings of patients with PCOS are predisposed to the occurrence of metabolic abnormalities partially similar to those observed in PCOS, expressed through impaired fasting glycemia, glucose intolerance and a more adverse lipid profile; however, they do not display the atherogenic dyslipidemia typical of PCOS. It seems that insulin resistance and atherogenic dyslipidemia in PCOS are related mainly to obesity and do not have a genetic background. To sum up, siblings of PCOS patients showing metabolic disturbances are a group at increased risk of cardiovascular and metabolic diseases, including type 2 diabetes, but this risk seems lower than in women with PCOS.

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Conflict of interest: None declared

Received: 12.10.2010
Revised: 15.11.2010
Accepted: 24.03.2011