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Cardiometabolic risk in patients with polycystic ovary syndrome

Ryzyko kardiometaboliczne u pacjentek z zespołem policystycznych jajników

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Abstract

Objectives: *Polycystic ovary syndrome (PCOS) is a common endocrinopathy in premenopausal women, associated with risk of metabolic syndrome and cardiovascular disease (CVD). CVD risk evaluation is recommended for PCOS patients. This study aimed to evaluate the risk of CVD in PCOS patients and to identify the best predictors for metabolic and cardiovascular disturbances.*

Material and methods: *The study included 169 PCOS patients and 110 healthy women in reproductive age. We estimated cardiovascular risk according to American Heart Association and Androgen Excess-PCOS Society criteria that classified patients as metabolically unhealthy (MU) or metabolically healthy (MH).*

Results: *The PCOS group had significantly higher body mass index (BMI), waist circumference, and waist-to-hip ratio (P<0.000001). Metabolic syndrome was only defined among PCOS patients (8.9%). No obesity was observed in the control group. Waist circumference ⩾80 cm was presented in 44% of PCOS patients in comparison to 14.5% of control participants (P<0.000001). There was a significant tendency for higher fasting insulin levels in the PCOS population (P<0.00001). Surprisingly, the PCOS-MH group had the highest high-density lipoprotein (HDL) levels. ROC curves were used to indicate parameters diagnosing metabolically unhealthy women and revealed that WC, BMI and HC seem to be the strongest predictors of metabolic disturbances in PCOS but in the healthy population in reproductive age biochemical findings such as low HDL or increased fasting glycemia presented stronger predictive value than patients' anthropometric features.*

Conclusions: *Physicians need to remember to adopt different diagnostic approach while seeking metabolic complications in these different groups of women.*

Key words: **metabolic syndrome** / **polycystic ovarian syndrome** / **insulin resistance** / / **cardiometabolic risk** /

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Streszczenie

Cel pracy: *Zespół policystycznych jajników (PCOS) jest częstym zaburzeniem endokrynologicznym w wieku reprodukcyjnym związanym z ryzykiem zespołu metabolicznego oraz choroby sercowo-naczyniowej (CVD). Ocena ryzyka sercowo-naczyniowego jest zalecana u kobiet z PCOS. Celem badania jest ocean ryzyka sercowo-naczyniowego u kobiet z PCOS oraz wskazanie najlepszych czynników predykcyjnych zaburzeń metabolicznych i sercowo-naczyniowych.*

Materiał i metody: *Badanie obejmowało 169 kobiet z PCOS i 110 zdrowych kobiet w wieku rozrodczym. Oceniono ryzyko sercowo-naczyniowe zgodnie z kryteriami American Heart Association and Androgen Excess-PCOS Society, które dzieliły pacjentki na metabolicznie zdrowe (MU) i metabolicznie chore (MH).*

Wyniki: *Grupa z PCOS miała znacząco wyższy indeks masy ciała (BMI), obwód talii, stosunek talia-biodro (P<0.000001). Zespół metaboliczny był jedynie obserwowany u kobiet z PCOS(8.9%). Nie obserwowano otyłości w grupie kontrolnej. Obwód talii≥80 cm obserwowano u 44% kobiet z PCOS i 14.5% w grupie kontrolnej (P<0.000001). W grupie PCOS była tendencja do wyższych poziomów insuliny(P<0.00001). Zaskakująco, grupa PCOS-MH miała najwyższy poziom high-density lipoprotein (HDL). Krzywe ROC użyte, aby wskazać parametry najlepiej identyfikujące kobiety metabolicznie chore, wskazały, że obwód talii, BMI i obwód bioder jest najlepszym predyktorem zaburzeń metabolicznych w PCOS. W zdrowej populacji kobiet w wieku rozrodczym, czynniki biochemiczne takie jak niski HDL lub podwyższony poziom glikemii lepiej przewidują zaburzenia metaboliczne niż parametry antropometryczne.*

Wnioski: *Lekarze muszą zwrócić uwagę, żeby w różnych grupach kobiet używać innych metod diagnostycznych do identyfikacji zaburzeń metabolicznych.*

Słowa kluczowe: **zespół metaboliczny** / **zespół policystycznych jajników** / / **insulinnooporność** / **ryzyko sercowo-naczyniowe** /

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, affecting 5–10% of this population [1, 2]. PCOS is characterized by irregular menstrual cycles and anovulation, polycystic ovarian structure on ultrasound, and excess androgen production [3].

Currently insulin resistance and abdominal obesity appear to be key factors in PCOS pathogenesis [3, 4]. They appear to play a substantial role in the higher risk of development of hypertension, cardiovascular disease, dyslipidemia, metabolic syndrome, and type 2 diabetes mellitus in this group of patients compared to the general population [5–8]. Metabolic syndrome constitutes a compilation of cardiovascular risk factors that are associated with dyslipidemia, obesity, impaired glucose tolerance, and hypertension [9]. It is also associated with a twofold increased risk of cardiovascular disease and fivefold increased risk of type 2 diabetes [10].

Therefore, the importance of identifying women at higher cardiometabolic risk and the prevention of cardiometabolic disease in these groups is being increasingly recognized [11]. Apridonidze et al. and Weerakiet et al. demonstrated higher rates of metabolic syndrome in women with PCOS than in age-matched women in the general population [12, 13]. The reported prevalence of metabolic syndrome in women with PCOS varies depending on the criteria used to define both PCOS and metabolic syndrome and ranges from 30% to 47% [14–16]. Mosca et al. reported that lifetime risk for cardiovascular disease in all women is high but mostly preventable, and thus concluded that all women should be screened for risk factors of cardiometabolic complications [17]. American Heart Association (AHA) published guidelines, which were further accepted by the Androgen Excess and Polycystic Ovary Syndrome Society (AE-PCOS), recommend that women with PCOS in particular should have their cardiovascular disease (CVD) risk evaluated and categorized [17, 18].

Aim of the study

The aim of this study was to evaluate the presence of cardiometabolic disturbances in women with PCOS compared to a group of healthy women and to estimate the severity of cardiometabolic risk in both groups. We also aimed to determine the parameters that are most predictive for these disturbances.

Materials and methods

This study included 169 women with PCOS, diagnosed according to Rotterdam criteria [19].

We evaluated in this group regularity of the cycles, signs of hyperandrogenism (evaluation of Ferrmiann-Gallway scale, signs of acne, acanthosis nigricans, seborrhea), as well as ultrasound image of the ovaries.

The control group consisted of 110 healthy women attending prophylactic gynecological visit in outpatient clinic, with regular menstrual cycles and lack of any diseases or drug usage that could interfere with the results. Patients recruited to the control group were taken into the study in the first phase of menstrual cycle (between the 3rd and the 5th day of the cycle). Theirs hormonal profile was controlled and lack of hormonal disturbances was confirmed.

All the patients were informed about the aims of the study and signed a consent form to take part in it. Measurements for the study were collected at the Department of Infertility and Reproductive Endocrinology of Poznan University of Medical Sciences between July 2012 and December 2013.

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The inclusion criteria into the study group were diagnosis of PCOS according to the Rotterdam criteria, age 18-43 and at least 4-month washout from contraceptive and antidiabetic drug use.

In both (control and the PCOS) groups, cardiovascular risk was estimated according to AHA and AE-PCOS criteria as follows:

"At risk"– women with any of the following risk factors:

1. Obesity (especially increased abdominal adiposity).
2. Cigarette smoking.
3. Hypertension.
4. Dyslipidemia (increased low-density-lipoprotein [LDL] cholesterol and/or non-high-density-lipoprotein [HDL]-cholesterol).
5. Subclinical vascular disease (increased visceral adipose index [VAI] >2,52 for women <30 years of age) [20].
6. Impaired glucose tolerance [21].
7. Family history of premature CVD (<55 years of age in male relatives, <65 year of age in female relatives).

"At high risk"– women with:

1. Metabolic syndrome.
2. Type 2 diabetes mellitus.
3. Overt vascular or renal disease [22].

Based on these criteria, patients in both the PCOS and control groups were categorized as metabolically unhealthy (MU), if they met "at risk" or "at high risk" criteria, or metabolically healthy (MH), if those risk factors were excluded [22]. In the PCOS group, we distinguished 97 PCOS-MU and 72 PCOS-MH patients, and in the control group, 51 CONTROL-MU and 59 CONTROL-MH subjects. Metabolic syndrome was diagnosed according to the 2009 revision of the International Diabetes Federation (IDF) definition [23].

All patients were evaluated according to their medical and family history as well as clinical examination, which included the measurement of body weight, height, waist circumference (WC) at the midpoint between the lateral iliac crest and the lowest rib margin at the end of normal expiration, hip circumference (HC) measured at the widest level of the greater trochanters, and waist-to-hip ratio (WHR). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Overweight was defined as a BMI between 25.0 and 29.9 kg/m^2, and obesity as BMI 30.0 kg/m^2 or higher, according to World Health Organization categories [24]. Patients were admitted for the hormonal analysis between the third and fifth days of the menstrual cycle.

Biochemical parameters were measured in the Central Laboratory of the University Hospital, which is a certified unit meeting ISO 9001 quality standards. In all subjects, blood samples for biochemical and hormonal analysis were drawn from the antecubital vein between 8–10 am after a 12-hour overnight fast. Samples that were not analyzed on the same day were centrifuged, the plasma aliquoted, and stored at -70°C until assayed.

All patients also underwent 75g oral glucose tolerance test (OGTT) to measure levels of insulin and glucose. Blood samples were obtained at baseline and at 30 minute intervals for 2 hours. The glucose level in venous blood was determined by means of the enzymatic (hexokinase) method with Roche Diagnostics laboratory reagents using a Hitachi 912 (Microparticle Enzyme Immunoassay, MEIA) AxSYM Insulin of Abbott. Glucose metabolism disturbances were diagnosed according to American Diabetes Association criteria [25]. As proper insulin values used for this paper authors arbitrary chose mean values got from metabolically healthy control group (MH control group = 5,4 mU/mL), and as pathological those that exceeded the 90 percentile for the MH-control group (10,4 mU/L).

Total serum cholesterol, HDL cholesterol, and triglycerides levels were measured with the appropriate reagents (Cholesterol CHOD-PAP, HDL-C plus, and Triglycerides GPO-PAP, respectively; Roche Diagnostics) using a Hitachi 912 analyzer, and LDL cholesterol level was calculated as total cholesterol – HDL cholesterol – TG/5.

The study was approved by the Bioethical Commission of Poznan University of Medical Sciences.

Distribution of variables was checked using the Shapiro-Wilk test and nonparametric tests, namely Mann-Whitney's U test and Kruskall-Wallis test were used for testing differences between or among analyzed groups, because the variables did not meet criteria for normal distribution. *P* values <0.05 were considered statistically significant. Results are expressed as median (range) unless otherwise stated. Statistical analysis was performed using Statistica software. Receiver operating characteristic (ROC) was used to determine a cutoff value for studied parametrs.

Results

In total, 168 patients with diagnosed PCOS and 110 healthy, regularly menstruating women were included in the study. All the demographic, clinical, and biochemical characteristics of both groups are shown in Table I including diagnostic criteria of metabolic syndrome, as well as AHA criteria for the risk of cardiovascular events. Looking at the biochemical profile we have found that all the parameters except fasting glucose levels were significantly different between both groups (Table II).

In the next step of our study we aimed to evaluate the frequency of various parameters estimating cardiovascular and metabolic risk in the studied groups (Table III). Patients in both groups had no family history of cardiometabolic events, and we found no significant difference in cigarette smoking frequency. Alarmingly, metabolic syndrome according to IDF criteria was present only in the PCOS group (8.9%). In the PCOS group, the prevalence of abnormally high BMI was 42.3%, with an obesity rate of 15.45%, while the control group had an 11.8% prevalence of abnormally high mean BMI with no obese subjects. Abdominal obesity was also very common in the study population, with 44% of PCOS patients having a waist circumference ≥80 cm, while only 14.5% in the control group had abdominal obesity (P<0.000001). Surprisingly we did not find any difference in HC between the groups. Although no patients suffered from diabetes mellitus or increased fasting glucose levels, we did notice a significant tendency for higher fasting insulin levels in the PCOS group (P<0.00001).

Table IV shows the clinical characteristics (including anthropometric measurements) and biochemical features of PCOS patients and controls divided according to AHA criteria. Interestingly there was no difference in the size of the groups. The PCOS-MU group had a significantly higher BMI than the other groups, with 39.2% of included patients being overweight and 37.1% obese.

Table I. The clinical and anthropometric measurements of PCOS group and control group.

	Control group	PCOS group	P [a]
N	110	168	
Age, years	28.5 [26.0-31.0]	27.0 [24.0-30.0]	0.004
BMI, kg/m2	20.5 [19,0-23,6]	24.2 [20.9-28.8]	0.000001
HC, m	87.9 [92.0-101.0]	97.0 [92.0- 108.0]	0.3
WC, m	69.5 [66.0- 74.0]	79.0 [70.0- 89.5]	0.000001
WHR	0.72 [0.7- 0.76]	0.78 [0.75- 0.80]	0.000001
VAI	2.1 [1.45-3.65]	2.55[2.2-2.81]	0.8

[a]*U-Mann Whitney test;*
A *P* value of <0.05 is considered statistically significant. Data are presented as median and interquartile range.
BMI: body mass index; HC: hip circumference; VAI: visceral adiposity index; WC: waist circumference; WHR: waist to hip ratio

Table II. Mean value of biochemical features in the PCOS and in the control group.

	Control group	PCOS group	P[a]
TC, mg/dL	170 [156-180]	188,4 [164.8-212.9]	< 0.00001
HDL, mg/dL	55 [45-63.5]	60.2 [49.7-71.2]	<0.001
TG, mg/dL	87 [78-94]	73.8 [57.9-107.0]	0.01
Fasting glucose, mg/dL	90 [84-96]	88,1 [83,0-93,9]	0.2
Fasting insulin, mU/ml	5.4 [46- 8.02]	7.6 [5.2-11.5]	0.000005

[a]*U Mann-Whitney test*
A *P* value of <0.05 is considered statistically significant. Data are presented as median [interquartile range].
HDL: high-density lipoprotein; TC: total cholesterol; TG: triglycerides;
Conversion factors to SI units are as follows: for TC, 0.0259; HDL, 0.0259; TG, 0.0113; fasting glucose, 0.0555; fasting insulin, 6.945

Table III. Frequency of selected parameters in the analysed groups.

	Control Group	PCOS Group	P[a]
Cigarette smoking	28 (25)	48 (28.57)	0.6
Family history of premature CVD (<55 years of age in female relative; <65 years of age in male relative)	0 (0)	0 (0)	
Metabolic syndrome	0 (0)	15 (8.)	0.001
Diabetes mellitus	0 (0)	0 (0)	
High blood pressure (≥130/85 mmHg)	0 (0)	0 (0)	
Increased triglycerides (≥1.7 mmol/l)	0 (0)	12 (7.1)	0.004
Decreased HDL-cholesterol (< 1.04mmol/l)	37 (33.6)	42 (25)	0.1
Increased WC (> 0,8 m)	16 (14.5)	74 (44)	0.00001
IFG	12 (10.9)	11(6.54)	0.2
Fasting insulin > 5.4 (mU/mL)	54 (49.1)	124 (73.8)	0.00001
Fasting insulin > 10.4 (mU/mL)	9 (8.2)	59 (35.1)	0.00001
BMI, kg/m²			
Underweight (< 18.50)	3 (2.7)	5 (3.0)	0.9[b]
Normal weight (18.50–24.99)	94 (85.4)	92(54.7)	0.0001
Abnormal weight (>24.99)	13 (11.8)	71 (42.3)	0.00001
Overweight (25.00–29.99)	13 (11.8)	45 (26.8)	0.003
Class I obesity (30.00–34.99)	0 (0)	15 (8.9)	0.001
Class II obesity (35.00–39.99)	0 (0)	10 (5.95)	0.009
Class III obesity (≥ 40.00)	0 (0)	1 (0.6)	0.4

[a] *– U-Mann Whitney test,* [b] *– test Ch-²*
A *P* value of <0.05 is considered statistically significant. Data are presented as number (percentage).
CVD: cardiovascular disease; HDL-cholesterol: high-density cholesterol; WC: waist circumference

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Table IV. The clinical characteristics (including anthropometric measurements) of four groups divided according to AHA criteria.

	PCOS- MH (1)	PCOS-MU (2)	Control-MH (3)	Control-MU (4)	P[a]
N (%)	71 (42.3)	97(57.7)	59 (53,6)	51 (46.4)	P=0.06
Age, years	26.9	27.4	28.5	29.4	1 vs.4 P<0.01; 2 vs. 4 P< 0.04; 1 vs. 2 P<0.01
BMI, kg/m^2	21.4	28.3	21.6	21.1	1 vs. 2 P<0.000001; 2 vs. 3 P < 0.00001; 2 vs. 4 P < 0.000001
HC, m	0.93	1.07	0.96	1.0	1 vs.2 P<0.000001; 1vs. 4 P<0.0001; 2 vs. 3 P<0.000001; 2 vs. 4 P<0.00007; 3 vs. 4 P= 0.004;
WC, m	0.71	0.88	0.69	0.75	1 vs. 2 P<0.000008; 1 vs. 4 P< 0.01; 1 vs. 3 P< 0.000008; 3 vs. 4 P< 0.0005 2 vs. 3 P<0.00001; 2 vs. 4 P<0.000001
WHR	0.76	0.82	0.72	0.73	ns
VAI	1.83	3.8	2.5	3.4	1 vs. 2 P<0.000008; 1 vs. 4 P<0.00002; 2 vs. 3 P<0.0005; 2 vs. 4 P< 0.00002
systolic blood pressure, mmHg	107.55	118.6	113.1	111.1	1 vs. 2 P< 0.000008; 2 vs. 3 P<0.04; 2 vs. 4 P< 0.003
diastolic blood pressure, mmHg	65.6	73.5	71.9	70.5	1 vs. 2 P< 0.00001; 1 vs. 4 P< 0.04; 1 vs. 3 P< 0.002

[a]Post-Hoc Analysis, Tukey's test
A *P* value of <0.05 is considered statistically significant. Data are presented as number (percentage) and median.
BMI: body mass index, HC: hip circumference; VAI: visceral adipozity index; WC: waist circumference; WHR: waist to hip ratio;

Table V. The metabolic profile of groups divided according to AHA criteria.

	PCOS- MH (1)	PCOS-MU (2)	Control-MH (3)	Control-MU (4)	P[a]
TC, mg/dL	190.1	188.1	170.4	169.3	1 vs. 3 P< 0.0004; 1 vs. 4 P < 0.0003; 2 vs. 3 P < 0.002; 2 vs. 4 P< 0.0005
HDL, mg/dL	74.3	53.6	60.7	49.0	1 vs. 2 P< 0.000008; 1 vs. 3 P< 0.000008; 1 vs. 4 P<0.000008; 3 vs. 2 P< 0.004; 2 vs. 4 P< 0.00002
TG, mg/dL	70.8	103.8	87.2	87.9	1 vs. 2 P< 0.000008; 1 vs. 3 P= 0.09; 1 vs. 4 P= 0.09, 2 vs. 3 P= 0.06; 2 vs. 4 P=0.01
LDL, mg/dL	101.7	111.9	78.6	82.9	1 vs. 2 P<0.02; 1 vs. 3 P< 0.000008; 1 vs. 3 P<0.00006; 2 vs. 3 P< 0.000008
TC/HDL	2.6	3.6	3.2	4.1	1 vs. 2 P<0.00001; 1 vs. 3 P< 0.02; 1 vs. 4 P< 0.000008; 2 vs. 4 P<0.02
Fasting glucose, mg/dL	85.0	90.7	86.7	92.8	1 vs. 2 P< 0.0009; 1 vs. 4 P< 0.00006; 3 vs. 4 P< 0.005
Fasting insulin, mU/ml	7.2	11.0	6.0	6.9	1 vs. 2 P< 0.0005; 2 vs. 3 P< 0.00001; 1 vs. 4 P< 0.0007; 2 vs. 4 P< 0.0007; 2 vs. 3 P< 0.0007

[a]Post-Hoc Analysis, Tukey's test
A *P* value of <0.05 is considered statistically significant. Data are presented as median.
Conversion factors to SI units are as follows: for TC, 0.0259; HDL, 0.0259; TG, 0.0113; LDL, 0.0259; fasting glucose, 0.0555; fasting insulin, 6.945
HDL-cholesterol: high-density lipoprotein cholesterol; LDL-cholesterol: low-denisty lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides;

In comparison, in the CONTROL-MU group only 7.8% of women were overweight, and 2.0% were obese. The PCOS-MU group was older than the PCOS-MH group but significantly younger than the CONTROL-MU group.

Table IV underlines the significant difference between the BMI, WC, and HC of PCOS-MU patients compared to other groups, with the highest frequency of obesity in PCOS-MU women. Surprisingly, there was no difference in WHR between the groups. We also observed the highest blood pressures in the PCOS-MU group, although no patient suffered from hypertension.

In all groups, the median values of lipid profile indices were within acceptable norms (Table V).

Table VI. Characteristics of ROC curves used for the identification of optimum cut-off values of IDF metabolic syndrome definition criterion used to diagnose metabolic syndrome in women with PCOS.

Test variable	Area under ROC curve	Optimal cut-off value	Sensitivity	Specificity
HDL, mg/dL	0.905 [0.865-0.937][a]	≤ 44	86.7	89.3
WC, m	0.890 [0.847-0.924][a]	>86	93.3	82.9
Diastolic BP, mmHg	0.875 [0.830-0.911][a]	>70	93.5	66.2
Systolic BP, mmHg	0.836 [0.788-0.878][a]	>120	66.7	81.4
TG, mg/dL	0.803 [0.752-0.849][a]	>98	80	77.8
Fasting glucose, mg/dL	0.698 [0.640-0.751][b]	> 98,4	46.7	89.4

[a]P<0.01 [b]P<0.0001
A *P* value of <0.05 is considered statistically significant. Data are presented as AUC [95% intervals]. Senisitivity and specificity are presented as percentage.
Conversion factors to SI units are as follows: for HDL, 0.0259; TG, 0.0113; fasting glucose, 0.0555;
AUC: area under the ROC curve; HDL-cholesterol: high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; WC: waist circumference.

Surprisingly, the PCOS-MH group had significantly higher HDL levels than the other groups. Table 5 also emphasizes once again the significant tendency for higher levels of fasting insulin in the PCOS groups.

In the next stage of the study, we attempted to determine which variable is the most valuable in predicting metabolic disturbances (Table VI). ROC curve analysis revealed that HDL presents the biggest AUC (0.905) in comparison to other parameters that also demonstrated high AUC values. The HDL cut-off value that most accurately predicted metabolic syndrome was ≤44 mg/dL. Notably, WC, which is an easy and cheap diagnostic parameter, also demonstrated high sensitivity and specificity in predicting metabolic syndrome (AUC=0.890). The weakest predictor of developing metabolic syndrome in our study was fasting glucose level (AUC= 0.698).

Various disturbances are known to occur long before the development of metabolic syndrome or cardiovascular events. Therefore, it is important to determine which parameters are the best predictors of the risk of metabolic disturbances. Among patients with PCOS, the anthropometric parameters of WC, BMI, and HC seemed to have the best predictive value for identifying metabolically unhealthy women (Table VII). Waist circumference had the biggest AUC (0.921) with an optimal cut-off value of >80 cm, the same as that used in the IDF metabolic syndrome definition. HDL also appeared to be a strong predictor of metabolic disturbances with a cut-off value of ≤47 mg/dl (AUC=0.855). In parallel, we assessed optimal cut-off points to identify metabolically unhealthy women in the control group. Unlike the PCOS group, in the control group, biochemical parameters were strong predictors to identify women with risk of metabolic disturbances, with HDL being the strongest risk predictor (AUC=0.847) (Table VIII).

Discussion

The present study aimed to evaluate the role of various clinical and biochemical parameters in predicting metabolic syndrome and early CVD in PCOS patients. For this purpose we investigated various anthropometric and laboratory markers of metabolic dysfunction potentially increasing the CVD risk in this group. There was a statistically significant difference in the age of the groups, with the control group older than the PCOS patients, which could potentially influence the increase of biochemical disturbances; however we did not observe this tendency in our control group. In all measured factors, patients belonging to the control group presented results closer to the established "healthy" levels.

Insulin resistance is a common but not essential feature of PCOS and is not always associated with an increased BMI. Many studies have shown that both lean and obese women with PCOS have increased insulin resistance [26], but recently it has been shown that in PCOS patients, insulin resistance is further worsened with increasing BMI [27]. Our study indicated a significant difference in fasting insulin level between metabolically unhealthy PCOS patients and metabolically healthy PCOS patients as well as metabolically unhealthy controls. Even if the level of fasting insulin was within normal range in both groups, we observed a tendency for higher levels in the PCOS-MU group.

In recent studies employing three different definitions of metabolic syndrome were used, the prevalence of metabolic syndrome surprisingly did not differ between women with PCOS and controls according to the IDF definition [27, 28].

Our study did not corroborate those findings, because the comparison of PCOS- MU and CONTROL-MU patients revealed a significant difference in BMI and WC between these groups. Studies by Apridonidze et al., Hahn et al., and Carmina et al. reported similar findings, with a higher prevalence of metabolic syndrome in women with PCOS when the IDF definition was used [12, 29, 30]; however the patients assessed in those previous studies also had higher BMI levels than patients in our study [29, 30]. Therefore, it is difficult to determine if PCOS may be an individual predictor of metabolic syndrome or if BMI and abdominal obesity are more important predictors of this disturbance. The reported prevalence of metabolic syndrome in women with PCOS varies ranges from 30% to 47% [15, 16, 31] depending on the criteria used to define both PCOS and metabolic syndrome. In our study, the 8.9% prevalence of metabolic syndrome was markedly lower than that in other studies. Thus, it is important to note that although both PCOS groups were heavier than the control groups in the present study, still they had lower BMI levels than reported in the patient populations of other studies [27, 28].

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Table VII. Characteristics of ROC curves used for the identification of optimum cut-off values to identify metabolically unhealthy patients in the group of PCOS patients.

Test variable	Area under ROC curve	Optimal cut-off value	Sensitivity [%]	Specificity [%]
WC, m	0.921 [0.870-0.957][a]	>80	76.30	100.00
BMI, kg/m^2	0.878 [0.818-0.923][b]	>23.67	79.38	85.92
HC, m	0.861 [0.800-0.91][b]	>100	68.00	88.70
HDL, mg/dL	0.855[0.792-0.904][b]	≤47	64.95	91.55
CHOL/HDL	0.797 [0.728-0.855][b]	>3.16	67.01	85.92
WHR	0.797 [0.728-0.855][b]	>0.79	62.90	85.90
Fasting insulin, mU/mL	0.779 [0.709-0.840][b]	>8.52	7.01	84.57
VAI	0.756 [0.684-0.819][b]	>2.27	63.92	0.28
Systolic BP, mmHg	0.727 [0.653-0.93][b]	>11	7.10	69.00
Diastolic BP, mHg	0.703 [0.628-0.771][b]	>60	77.30	53.50
TG, mg/dL	0.673 [0.597-0.744][b]	>91.2	51.55	84.51
Fasting glucose, mg/dL	0.671 [0.594-0.741][b]	>91.6	48.45	80.28
LDL, mg/dL	0.593 [0.514-0.668][d]	>129.5	28.90	91.40
Age, years	0.541 [0.462-0.618][c]	>29	36.10	77.50
TC, mg/dL	0.526 [0.448-0.603][e]	≤156.8	21.65	91.15

Table VIII. Characteristics of ROC curves used for the identification of optimum cut-off values to identify metabolically unhealthy patients in the control group.

Test variable	Area under ROC curve	Optimal cut-off value	Sensitivity	Specificity
HDL, mg/dL	0.847 [0.705-0.909][a]	≤49	72.50	100.00
VAI	0.844 [0.761-0.907][a]	>2.9	72.50	87.50
CHOL/HDL	0.797 [0.708-0.869][a]	>3.392	76.47	87.50
Fasting glucose, mg/dL	0.683 [0.587-0.769][c]	>89.1	68.60	63.80
WHR	0.682 [0.586-0.768][f]	>0.73	52.90	74.14
WC, m	0.682 [0.586-0.768] [d]	>71	56.90	79.30
HC, m	0.624 [0.526-0.715][e]	>99	47.10	86.20
LDL, mg/dL	0.598 [0.498-0.691][b]	>74	76.50	39.30
BMI, kg/m^2	0.579 [0.480-0.674][b]	≤18.9	25.50	91.10
Age, years	0.559 [0.461-0.654][b]	>29	49.20	66.50
TC, mg/dL	0.551 [0.452-0.647][b]	≤164	41.20	71.40
Fasting insulin, mU/ml	0.548 [0.480-0.644][b]	>3.93	88.00	24.10
Systolic BP, mmHg	0.547 [0.449-0.643][b]	≤100	35.30	75.90
Diastolic BP, mmHg	0.533 [0.435-0.629][b]	≤75	70.60	43.10
TG, mg/dL	0.518 [0.419-0.616][b]	>65	100.00	8.90

PCOS is known to predispose patients to increased weight and mainly abdominal obesity [12, 30, 31]. Abdominal fat excess is also known to be associated with increased risk of atherosclerosis [34] and CVD mortality [35].

Our study aimed to determine not just whether PCOS patient and control populations differed in metabolic status, but also which parameters were most valuable in predicting the risk of impaired metabolic status. We found that the PCOS group had significantly higher abdominal obesity measured by WC, and WHR also differed between these groups. However, when groups were compared according to AHA risk criteria, there was no difference in WHR, indicating that WC alone is useful to predict metabolic disturbances. A Dutch study on women with PCOS also reported that increased WC was a powerful predictor of the presence of metabolic syndrome and insulin resistance [36].

Our finding of a correlation between central obesity and the presence of metabolic disturbances in PCOS is in agreement with an earlier study published by Janssen et al., who concluded that WC is more closely related with obesity-related risk factors than BMI [37]. Our study, like the National Health and Nutrition Examination Survey (NHANES III study), indicated that WC predicts cardiometabolic risk as well as the development of metabolic syndrome better than BMI, but mainly in PCOS patients [31,38]. Our study also supports the reports that WC seems to be an independent risk factor for developing metabolic syndrome in PCOS patients and is more strongly predictive than

other parameters such as elevated LDL cholesterol or triglycerides [38, 39]. Overall, our study indicates that BMI and WC, which are easy to measure, constitute parameters with good predictive ability for metabolic disturbances in this group of PCOS patients.

By contrast, our results confirmed that in the general population, biochemical features such as disturbed lipid profile and increased fasting glucose were more accurate than overweight status in predicting CV risk, as has been previously reported by other authors [37, 38]. It is important to remember that obesity in the general population may not always exist with any tangible cardiometabolic disturbances, as in the state called "metabolically healthy obesity" [40]. In the general population, therefore, biochemical findings such as low levels of HDL or elevated fasting glycemia seem to be very strong predictors of metabolic syndrome and cardiovascular risk. However, in the study presented by Shroff et al., no participants from the control group with BMI < 30 presented metabolic syndrome [41]. This observation may confirm the role of general obesity as well as abdominal obesity as separate, important determinants of metabolic syndrome independent of other cardiovascular risk factors [42].

In addition to all the previously studied parameters, we also assessed whether VAI is a suitable factor for predicting metabolic abnormalities in PCOS. Contrary to the study of Androulakis et al., which showed elevated VAI in PCOS patients, our results did not demonstrate a statistical difference between the PCOS and control groups. This parameter was also not a very strong predictor of metabolic disturbances within the PCOS group, but was found to be very suitable for indicating metabolically unhealthy women in the general population.

Conclusion

The strength of the present study is the fact that examined parameters are easy, fast and cheap to measure, thus the results of our study may be useful in general practices for diagnosing at risk patients. Results from study must be viewed cautiously due to its own limitations.

Firstly, we only selected Caucasian population, we can not generalize the results to the general population, and thus it might be crucial to perform similar studies in other ethnic groups.

Secondly it would be useful to enlarge the study and control group, as well to make those groups more comparable according to age.

Additional studies with follow-up after medical treatment, dietary and lifestyle modifications would be interesting. However, difficulties such as budget limitations and lower compliance of participants in lifestyle modification trials may provide challenges.

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2. Leszek Pawelczyk – współautor protokołu, korekta i aktualizacja literatury, korekta i akceptacja ostatecznego kształtu manuskryptu.

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