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Circulating vaspin levels and nutritional status and insulin resistance in polycystic ovary syndrome

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ABSTRACT

Objectives: The study aimed to assess the associations between circulating vaspin levels and nutritional status (assessed on tha basis of BMI) as well as insulin resistance in PCOS.

Material and methods: Eighty-seven PCOS women, 48 obese and 39 normal weight, were enrolled in the cross-sectional study. Seventy-two Non-PCOS women, 41 obese and 31 normal weight, constituted a control group. Body mass, height and waist circumference as well as body composition by bioimpedance were measured. In the morning (16h after the last meal) we determined: serum glucose, insulin, androgens, gonadotropin (LH, FSH) and sex hormone-binding globulin (SHBG) as well as plasma vaspin levels. Standard HOMA-IR formula was used to assess insulin resistance (IR).

Results: Plasma vaspin levels were significantly lower in PCOS, both normal weight and obese, than in Non-PCOS groups. Vaspin levels were similar in normal weight and obese PCOS subgroups. There was no association between plasma vaspin levels and anthropometric parameters in PCOS group. While in Non-PCOS group a negative correlation between plasma vaspin levels and body mass ($r = -0.26$; $p < 0.05$) was found. We did not observe correlations between plasma vaspin levels and serum glucose and insulin concentrations as well as HOMA-IR values, however, in multivariable, stepwise backward regression waist circumference and HOMA-IR values explained 18.0% of plasma vaspin levels variability in the study subjects.

Conclusions: PCOS occurrence is associated with decreased vaspin levels. The influence of nutritional status on vaspin level observed in Non-PCOS is abolished in PCOS women, possibly by more severe insulin resistance.

Key words: vaspin; insulin resistance; nutritional status; PCOS

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INTRODUCTION

Vaspin is an adipokine, the member of the serine protease inhibitors family (serpin) [1]. Vaspin mRNA expression was found in subcutaneous and visceral adipose tissue, liver, pancreas, stomach and skin [2–5].

The experimental studies have shown that vaspin increased insulin sensitivity and glucose tolerance as well as decreased food intake [4, 6]. Expression of vaspin mRNA in rats visceral adipose tissue increased with an excess of body mass and insulin resistance [1]. In addition, factors

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stimulating vaspin expression were leptin and metformin and inhibiting night break in food intake [7].

In the human expression of vaspin mRNA in visceral adipose tissue was proportional to BMI value and body fat percentage. In turn, this expression in subcutaneous adipose tissue was proportional to WHR values and fasting serum insulin levels [2]. The association between plasma vaspin levels and BMI values and insulin resistance was also shown in another study [8]. Plasma vaspin levels were higher in women than in men [8]. It is suggested that this sex difference develops during puberty [3]. However, in subjects with metabolic and cardiovascular disturbances the association between circulating vaspin levels and BMI values, sex and age were not observed [9, 10].

It has been suggested that increase vaspin mRNA expression and its secretion are a compensatory mechanism that delays insulin resistance development [2, 8, 11]. However, the results of other studies did not confirm this hypothesis [10–13].

Several projects assessing vaspin levels in PCOS showed inconclusive results. Higher vaspin levels were observed in normal-weight PCOS than in Non-PCOS women [14–16]. On the other hand, there were no differences between overweight/obese PCOS and Non-PCOS women [16]. In addition, serum testosterone levels, FAI values and mean ovary volume or the number of follicles were proportional to vaspin levels. While serum FSH and SHBG levels, as well as insulin sensitivity, were inversely related to vaspin levels [16]. The highest plasma vaspin levels were shown in the phenotype A, thus this parameter is considered as the marker of the severity of PCOS [17]. The lack of differences between plasma vaspin levels in adolescents with or without PCOS has also been shown [18]. Similarly, vaspin levels did not differ between normal-weight PCOS and Non-PCOS women in Iranian population, despite higher insulin levels in PCOS group [19]. In turn, treatment with metformin and improvement of the insulin sensitivity caused a decrease in vaspin levels [14]. However, Koiou et al. [16] have shown only a slight effect of treatment with metformin on vaspin levels in normal-weight PCOS women and lack of the impact of moderate weight loss on vaspin levels in overweight and obese PCOS women.

The study aimed to assess the associations between circulating vaspin levels and nutritional status (assessed on the basis of BMI) as well as insulin resistance in PCOS.

MATERIAL AND METHODS

Eighty-seven PCOS (diagnosed on the basis of Rotterdam ESHRE/ASRM criteria [20]) women, 48 obese and 39 normal-weight, were enrolled in the cross-sectional study. Seventy-two Non-PCOS women, 41 obese and 31 normal weight, constituted the control group. The exclusion criteria included any pharmacotherapy, alcohol and nicotine addiction and changes of body mass over 2 kg during the last 3-months. The written informed consent was obtained from all subjects. The Bioethical Committee of the Medical University of Silesia approved the study protocol.

Nutritional status was diagnosed on the basis of BMI values in accordance with World Health Organization criteria. Table 1 presents the characteristics of the study and control groups.

The venous blood samples (15 mL) for laboratory tests were collected in the morning 16 hours after the last meal

Table 1. Patients characteristics'

	PCOS			non-PCOS		
	All (n = 87)	**Normal weight (n = 39)**	**Obese (n = 48)**	**All (n = 72)**	**Normal weight (n = 31)**	**Obese (n = 41)**
Age [years]	25.4 ± 5.5	23.7 ± 4.5^{++}	26.8 ± 5.8	26.4 ± 5.5	23.8 ± 4.3$^{\$\$\$}$	28.4 ± 5.6
Body mass [kg]	79.4 ± 26.4	56.9 ± 11.7^{***+++}	97.7 ± 20.2$^{\&\&\&}$	78.7 ± 20.4	59.8 ± 7.1$^{\$\$\$}$	93.1 ± 14.6
BMI [kg/m^2]	28.6 (20.8–35.7)	20.6^{***+++} (19.6–22.7)	35.1$^{\&\&\&}$ (31.3–40.2)	28.5 (22.9–33.5)	22.4$^{\$\$\$}$ (21.0–24.0)	32.9 (30.3–36.7)
Body fat [kg]	30.2 (15.4–42.6)	15.0^{**++} (12.6–19.7)	40.6$^{\&\&}$ (33.4–56.3)	33.3 (19.1–50.4)	18.1$^{\$\$}$ (14.8–20.6)	49.4 (37.5–50.2)
Body fat [%]	38.1 (27.5–45.7)	26.5^{***+++} (24.2–31.0)	44.8$^{\&\&\&}$ (41.9–51.1)	40.6 (30.4–48.5)	30.0$^{\$\$\$}$ (26.8–33.9)	46.8 (42.3–51.4)
Waist circumference [cm]	89.8 ± 18.7	72.6 ± 7.3^{***+++}	103.7 ± 12.3$^{\&\&\&}$	87.9 ± 18.2	70.5 ± 8.3$^{\$\$\$}$	101.0 ± 11.3
Total cholesterol [mg/dL]	176.3 ± 34.0	167.7 ± 28.1*	183.2 ± 37.0	174.6 ± 30.6	169.1 ± 33.3	178.8 ± 27.5
LDL- cholesterol[mg/dL]	105.4 ± 38.3	93.8 ± 27.5**	115.1 ± 37.6	100.3 ± 27.1	90.3 ± 31.9	106.4 ± 21.9
HDL- cholesterol [mg/dL]	45.7 ± 14.1$^{\%\%\%}$	48.1 ± 15.1$^{*\#\#}$	43.8 ± 12.9$^{\&\&\&\wedge\wedge\wedge}$	57.1 ± 15.2	60.1 ± 16.3$^{\$}$	54.8 ± 14.2
Triglycerides [mg/dL]	100.7 ± 55.2	73.0 ± 31.7$^{**\#\#}$	121.5 ± 61.4$^{\&\&\wedge\wedge}$	80.1 ± 32.1	67.2 ± 26.7$^{\$\$}$	89.9 ± 32.6
Glucose [mmol/L]	5.1 ± 0.8$^{\%\%\%}$	4.9 ± 0.7$^{\#\#}$	5.3 ± 0.9$^{\&\&\wedge\wedge}$	4.7 ± 0.4	4.7 ± 0.5	4.7 ± 0.4
Insulin [µIU/mL]	10.6$^{\%\%}$ (7.8–15.1)	8.4** (6.0–10.6)	12.9$^{\&\&\wedge\wedge}$ (9.7–18.6)	7.4 (5.9–9.5)	6.8 (5.6–8.7)	7.8 (6.3–10.0)
HOMA-IR	2.3$^{\%\%}$ (1.6–3.2)	1.8** (1.2–2.3)	2.8$^{\&\&\wedge\wedge}$ (1.2–4.1)	1.5 (1.2–2.0)	1.5 (1.1–1.9)	1.7 (1.4–2.2)

$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ normal weight PCOS vs obese PCOS; $^{\#}p < 0.05$; $^{\#\#}p < 0.01$; $^{\#\#\#}p < 0.001$ normal weight PCOS vs normal weight non-PCOS; $^{+}p < 0.05$; $^{++}p < 0.01$; $^{+++}p < 0.001$ normal weight PCOS vs obese non-PCOS; $^{\&}p < 0.05$; $^{\&\&}p < 0.01$; $^{\&\&\&}p < 0.001$ obese PCOS vs normal weight non-PCOS; $^{\wedge}p < 0.05$; $^{\wedge\wedge}p < 0.01$; $^{\wedge\wedge\wedge}p < 0.001$ obese PCOS vs obese non-PCOS; $^{\$}p < 0.05$; $^{\$\$}p < 0.01$; $^{\$\$\$}p < 0.001$ normal weight non- PCOS vs obese non-PCOS; $^{\%}p < 0.05$; $^{\%\%}p < 0.01$; $^{\%\%\%}p < 0.001$ all PCOS vs all non-PCOS

between 3–5 days of the menstrual cycle. Height, body mass and waist circumference were measured. BMI was calculated. The bioimpedance method (Bodystat 1500, Douglas, Isle of Man) was used to the assessment of body composition.

Serum and plasma samples were stored frozen in –70°C.

Laboratory procedures

Calorimetric methods (kits made by Roche, Switzerland) were used to determine serum glucose and lipids. Fasting serum insulin levels were measured by enzyme-linked immunosorbent assay — ELISA (DRG Instruments GmbH, Marburg, Germany) with a lower limit of detection of 1.76 μIU/mL. The insulin resistance was assessed on the basis of HOMA-IR = fasting concentration of insulin (μIU/mL) × fasting concentration of glucose (mmol/L)/22.5.

The ELISA (DRG Instruments GmbH, Marburg, Germany) method was also used to determine concentrations of gonadotropin (FSH, LH), prolactin (PRL), estradiol (E_2), androgens (testosterone, free testosterone, androstenedione, DHEA-S) as well as plasma vaspin levels (BioVendor, Brno, The Czech Republic) with the lower limit of detection of 0.01 ng/mL and intra-assay coefficient variation 7.6% and inter-assay coefficients variation 7.65%.

In addition, with the standard formula, the free androgen index (FAI) was calculated.

Statistic analysis

STATISTICA 9.0 PL (StatSoft Poland) software and R software environment were used for statistical analysis. There was no missing data in the database. The mean values ± standard deviation and median with upper and lower quartiles were used for the presentation of the results. The D'Agostino-Pearson test was used to assess the distribution of variables. The Levene test was used to assess the homogeneity of variances. Two-way multivariable analysis of variances with Duncan *post-hoc* test was used for comparison of quantitative variables. The multivariable linear regression with the backward stepwise procedure was used to assess the associations between variables. Cook's distance values were used for identification of outliers. Testing the residuals for heteroskedasticity was performed using the Cook-Weisberg test. Models calculation was performed including evaluation of multicollinearity, which was assessed with the variance inflation factor (VIF below 5). Additionally, how well it fit in the obtained model was also assessed with the F test and determination coefficient R^2. Values below 0.05 were considered statistically significant.

RESULTS

Body mass and BMI values were similar in the corresponding PCOS and Non-PCOS subgroups. Significantly higher glucose and insulin levels as well as HOMA-IR and FAI values and lower HDL cholesterol and SHBG levels were found in PCOS in comparison to Non-PCOS group and obese than normal-weight PCOS subgroups (Tab. 1 and 2).

Plasma vaspin levels were significantly lower in PCOS than in Non-PCOS group. The lower plasma vaspin levels were shown in both PCOS and in the corresponding Non-PCOS subgroups. Similar plasma vaspin levels were found in normal weight and obese PCOS subgroups, while

Table 2. Serum concentrations of hormones and plasma vaspin levels in analyzed groups of PCOS and non-PCOS

	PCOS			non-PCOS		
	All (n = 83)	**Normal weight (n = 39)**	**Obese (n = 48)**	**All (n = 72)**	**Normal weight (n = 31)**	**Obese (n = 41)**
FSH [mIU/mL]	5.7 (4.4–7.4)	5.5 (4.5–6.6)	5.9 (4.4–8.5)	5.4 (3.9–6.8)	5.4 (3.5–6.5)	5.5 (4.3–7.1)
LH [mIU/mL]	10.0$^{\%\%}$ (6.6–14.4)	8.2 (5.2–12.8)	10.9$^{\&\&}$ (8.2–15.6)	8.0 (6.0–12.2)	7.7 (6.4–9.2)	9.1 (4.0–15.4)
LH/FSH	1.7$^{\%}$ (1.1–2.5)	1.6* (1.0–2.4)	1.7$^{\wedge}$ (1.2–2.6)	1.5 (0.9–2.5)	1.5 (1.1–2.5)	1.5 (0.6–2.5)
PRL [ng/mL]	5.9$^{\%\%\%}$ (4.1–8.3)	4.6$^{\#\#++}$ (3.5–7.7)	6.8 (4.9–8.5)	8.1 (5.2–10.7)	7.8 (6.2–12.0)	8.4 (4.7–10.2)
Androstendione [ng/mL]	2.2 (1.5–3.3)	2.8$^{**\#\#++}$ (2.1–3.6)	1.9 (1.3–2.8)	1.9 (1.4–2.8)	2.1 (1.4–3.1)	1.8 (1.4–2.6)
DHEA-S [μg/mL]	2.7 (2.1–3.5)	2.7 (2.2–3.5)	2.8 (2.1–3.4)	2.6 (1.8–3.5)	2.7 (2.1–3.9)	2.4 (1.7–3.3)
Total testosterone [ng/mL]	0.7 (0.5–0.9)	0.7 (0.5–0.9)	0.6 (0.5–0.8)	0.6 (0.4–0.8)	0.6 (0.4–0.8)	0.6 (0.4–0.8)
Free testosterone [pg/mL]	1.8$^{\%}$ (1.1–2.8)	2.1$^{*\#+}$ (1.4–3.1)	1.6 (1.1–2.6)	1.4 (0.8–2.3)	1.4 (0.9–2.3)	1.4 (0.8–2.3)
Estradiol [pg/mL]	41.9 (29.6–66.7)	43.6 (32.7–72.6)	40.0 (27.1–64.1)	56.5 (29.7–90.7)	56.8 (34.4–82.7)	54.9 (24.6–111.4)
SHBG [nmol/l]	23.0$^{\%\%}$ (14.8–37.3)	34.2^{**++} (17.3–49.9)	19.0$^{\&\&}$ (10.8–26.7)	30.7 (20.4–49.0)	38.6$^{\$\$}$ (28.2–63.6)	22.9 (16.5–47.3)
FAI	3.1$^{\%\%}$ (1.7–4.9)	2.3$^{**\#+}$ (1.2–4.4)	3.3$^{\&}$ (2.0–5.1)	1.7 (1.1–3.1)	1.5$^{\$}$ (0.9–2.2)	2.0 (1.3–4.4)
Vaspin [ng/mL]	0.13 (0.03–0.87)	0.13$^{\#\#+++}$ (0.04–0.87)	0.13$^{\&\&\wedge\wedge\wedge}$ (0.03–0.53)	0.18 (0.03–2.07)	0.16$^{\$}$ (0.03–1.38)	0.19 (0.06–2.07)

*p < 0.05; **p < 0.01; ***p < 0.001 normal weight PCOS vs obese PCOS; $^{\#}$p < 0.05; $^{\#\#}$p < 0.01; $^{\#\#\#}$p < 0.001 normal weight PCOS vs normal weight non-PCOS; $^{+}$p < 0.05; $^{++}$p < 0.01; $^{+++}$p < 0.001 normal weight PCOS vs obese non-PCOS; $^{\&}$p < 0.05; $^{\&\&}$p < 0.01; $^{\&\&\&}$p < 0.001 obese PCOS vs normal weight non-PCOS; $^{\wedge}$p < 0.05; $^{\wedge\wedge}$p < 0.01; $^{\wedge\wedge\wedge}$p < 0.001 obese PCOS vs obese non-PCOS; $^{\$}$p < 0.05; $^{\$\$}$p < 0.01; $^{\$\$\$}$p < 0.001 normal weight non- PCOS vs obese non-PCOS; $^{\%}$p < 0.05; $^{\%\%}$p < 0.01; $^{\%\%\%}$p < 0.001 all PCOS vs all non-PCOS

lower plasma vaspin levels were observed in normal-weight than in obese Non-PCOS subgroups (Tab. 2).

Correlation between plasma vaspin levels and anthropometric parameters and insulin resistance

We did not observe any association between plasma vaspin levels or any anthropometric parameters in all study groups and the PCOS group. While in Non-PCOS group the negative correlation between plasma vaspin levels and body mass ($r = –0.26$; $p < 0.05$).

There was no correlation between plasma vaspin levels and serum glucose and insulin concentrations as well as HOMA-IR values in both all study groups and both PCOS and Non-PCOS groups analyzed separately.

Multivariable regression analyses

Multivariable, stepwise backward regression analyses revealed that waist circumference but no other anthropometric parameters, as well as HOMA-IR values, explained 18.0% of plasma vaspin levels variability.

DISCUSSION

The results presented in this study demonstrate lower vaspin levels in PCOS women in corresponding, according to nutritional status, Non-PCOS subgroups. In addition, vaspin levels were affected by measures of nutritional status, but only in Non-PCOS subgroup. They were inversely proportional to body mass, and lower in normal weight than obese Non-PCOS.

It should be noted, that it is the first study that showed lower vaspin levels in PCOS women independently from nutritional status. In four published studies higher vaspin levels in PCOS women were described [14–17] and in two there were no differences between PCOS and Non-PCOS subjects [18, 19]. In addition, we found striking differences in vaspin levels in previously published studies. Only in one study performed in 12 subjects the median of vaspin levels was similar to obtained in our study [14]. While in Turkish subjects mean vaspin levels were more than two times higher in PCOS group and in the control group almost five times lower than in our study [15]. Similar, differences were observed in Greek cohorts [16].

Contrary, to previously published studies [17] in multiple regression analysis we observed an inverse association between vaspin levels and waist circumference in PCOS subjects. In addition, contradictory to the other studies, we did not observe an association between vaspin levels and BMI values [8, 17]. These differences are difficult to explain. On the one hand, it may be a result of small study group sizes [14, 15], the differences in nutritional status between study and control groups (mean BMI 5 kg/m^2 lower in control group) [16, 17] and race. On the other hand, it may be the result of different ELISA kits used to vaspin levels measurements, produced by different manufacturers. The lack of studies comparing specificity of kits produced for vaspin levels assessment should be raised.

Furthermore, we did not observe the association between serum glucose and insulin concentrations as well as HOMA-IR values and circulating vaspin levels. It is opposite to some published studies that show that HOMA-IR values were proportional to vaspin levels in PCOS women [17–19] but in accordance with the results of other studies [15, 17]. The association between insulin resistance or glucose metabolism and circulating vaspin levels is not clear. It should be noted that only Youn et al. [8] shown an association between HOMA-IR and vaspin levels in group with normal glucose tolerance. In addition, Tan et al. [14] found that vaspin synthesis is stimulated by glucose in omental adipocytes. Moreover, vaspin mRNA expression but not its circulating levels were proportional to insulin resistance. Therefore, we hypothesized that increased vaspin levels may be a compensatory mechanism in the development of the early stage of insulin resistance, that run out over time. This hypothesis is partially supported by the observed lower vaspin levels in PCOS subjects and its higher levels in obese than normal-weight Non-PCOS women. However, further studies with follow-up are necessary to confirm our hypothesis.

The main limitations of the study are the small sizes of study subgroups and the lack of the assessment of the body fat visceral and subcutaneous using DEXA or CT scanner. Additionally, only selected adipokine vaspin was analyzed thus the assessment of the association between hormonal disturbances of adipose tissue and it's inflammation was not possible.

CONCLUSIONS

PCOS occurrence is associated with decreased vaspin levels in young women. The influence of nutritional status on vaspin level observed in Non-PCOS is abolished in PCOS women, possibly by the coexisting insulin resistance.

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