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Serum asprosin level in different subtypes of polycystic ovary syndrome: a cross-sectional study

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SUMMARY

OBJECTIVE: Polycystic ovary syndrome can be divided into different subtypes, including insulin resistance and hyperandrogenism. The aim of this study was to investigate the relationship between serum asprosin levels and polycystic ovary syndrome subtypes.

METHODS: A total of 93 women with polycystic ovary syndrome and 77 healthy women as controls were selected for this study. The clinical and laboratory data were compared between the Polycystic ovary syndrome group and the control group. The Polycystic ovary syndrome group was further divided into subgroups: (1) women with or without hyperandrogenism (polycystic ovary syndrome hyperandrogenism and Polycystic ovary syndrome none-hyperandrogenism, respectively) and (2) women with or without insulin resistance (polycystic ovary syndrome insulin resistance and Polycystic ovary syndrome none-insulin resistance, respectively). Serum asprosin was measured by using enenzyme-linked immunosorbent assay.

RESULTS: Serum asprosin levels showed no significant difference between the polycystic ovary syndrome and control groups. However, it was significantly lower in the Polycystic ovary syndrome HA and insulin resistance groups compared with the respective Polycystic ovary syndrome none-hyperandrogenism and none-insulin resistance groups ($p<0.05$). In the Polycystic ovary syndrome group, serum asprosin was negatively correlated with body mass index, luteinizing hormone, testosterone, basal antral follicles, fasting insulin, homeostatic model assessment of insulin resistance, and triglycerides. After adjusting for body mass index, the correlations were not significant, and asprosin was only positively correlated with prolactin (prolactin; $r=0.426$, $p<0.001$).

CONCLUSION: Our study shows that women with polycystic ovary syndrome hyperandrogenism or insulin resistance exhibit significantly lower serum asprosin levels compared with controls, and the lower asprosin level directly correlated with prolactin level.

KEYWORDS: Hyperandrogenism. Insulin resistance. Asprosin protein.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common and complex endocrine metabolic disease caused by genetic and environmental factors. PCOS is mainly characterized by menstrual abnormalities, infertility, hyperandrogenism (HA), polycystic ovarian morphology (PCOM), and metabolic abnormalities. Metabolic abnormalities are often manifested as obesity, insulin resistance (IR), and dyslipidemia[1,2]. PCOS increases the risk for type 2 diabetes mellitus (T2DM), gestational diabetes, as well as other pregnancy-related complications, cardiovascular events, and endometrial cancer[3]. IR is considered as the major risk factor for the onset of PCOS, and 70% of patients with PCOS have shown signs of IR[4]. It has also been demonstrated that aging affects the metabolic phenotype of PCOS, and therefore, age matching or correcting for age is important for PCOS studies[5].

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Asprosin, a recently identified hormone, is secreted by the white adipose tissue (WAT)[6]. It is a 140-amino-acid fragment from the C-terminal of profibrillin (encoded by FBN1) and induces the liver to increase the levels of plasma glucose. Earlier studies showed that asprosin was pathologically elevated in humans and mice with IR or obesity[6]. The olfactory receptor OLFR734 specifically binds with asprosin to modulate hepatic glucose production[7]. Several recent studies have shown that asprosin correlated with obesity in children and adults, T2DM and PCOS[8-10]. However, these results have been inconsistent. Thus, the aim of this study was to explore the potential relationship of asprosin with PCOS in women, especially those with HA or IR.

METHODS

Study subjects

This study retrieved 170 serum samples, including 93 from PCOS group and 77 from those without PCOS for the control group. The samples were obtained from the biobank affiliated to the Center for Reproductive Medicine of Shandong University. All serum samples were donated from infertility-related patients and were stored at -80°C. PCOS was diagnosed by following the Rotterdam diagnostic criteria[11]. Two of the following three criteria were positive, after the exclusion of other etiologies: (1) oligoovulation and/or anovulation, (2) clinical and/or biochemical signs of HA, and (3) polycystic ovaries on ultrasonography. The exclusion criteria included women having androgen-secreting tumors, hyperprolactinemia, 21-hydroxylase deficiency (21-OHD), Cushing's syndrome, congenital adrenal hyperplasia, thyroid disease, and abnormal intrauterine cavity. A history of recurrent spontaneous abortion, intake of medications, antidiabetic drugs, antiandrogens, oral contraceptives, insulin sensitizers, glucocorticoids, and ovulation induction agents were also excluded. The threshold for defining PCOM on ultrasound was the presence of 12 or more follicles measuring 2–9 mm in diameter or an increased ovarian volume (>10 mL) in at least one ovary. The controls were age-matched women who had infertility related to male factors or tube factors, during the same period in our *in vitro* fertilization program. PCOS was divided into subtypes according to testosterone (T) levels and homeostasis model of assessment for insulin resistance index (HOMA-IR): PCOS with HA (PCOS HA, T>60 ng/dL) and without HA (PCOS NHA) and PCOS with IR (PCOS IR, HOMA-IR≥2.5) and without IR (PCOS NIR)[12,13]. All the serum samples were collected in the follicular phase.

Clinical and laboratory data collection

The clinical and laboratory data were collected from electronic medical records (EMR) in our hospital. The anthropometric data included height, weight, body mass index (BMI), and menstrual cycle history. Serum hormones measured included follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin (PRL), testosterone (T), thyroid-stimulating hormone (TSH), dehydroepiandrosterone sulfate (DHEA-S), and anti-Müllerian hormone (AMH), and these were tested using electrochemiluminescence. Basal antral follicles were counted between the 3rd day and 5th day of menstruation by vaginal ultrasonic examination. Metabolic-related indicators including fasting glucose, fasting insulin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) were measured. HOMA-IR was calculated as fasting glucose (in mmol/L) × fasting insulin (in mIU/L)/22.5.

Measurement of asprosin

Serum asprosin was measured using a commercial human asprosin ELISA Kit (Catalog No: E15190h, Wuhan EIAab Science Co. Ltd., China) according to the manufacturer's instructions. In brief, 100 µL serum covered with the plate sealer was incubated at 37°C for 2 h. First, the liquid was then removed, and 100 µL of detection reagent A was added and incubated at 37°C for 1 h. Second, the sample was washed 3 times, and 100 µL of detection reagent B was added. After 1-h incubation, the sample was washed 5 times, and 90 µL of substrate solution was added. Of note, 50 µL of stop solution was then added, and optical density of 450 nm was determined by automated microplate reader (PerkinElmer, Inc., Waltham, MA, USA). The acquired data were calculated by CurveExpert 1.4 (Hyams D.G., Starkville, MS, USA). The intra-assay coefficient of variation (CV) was ≤6.5%, and the inter-assay CV was ≤9.8%.

Statistical analysis

All the statistical analyses were conducted using the SPSS software (IBM, Armonk, NY, version 21.0) and GraphPad Prism 7 software (San Diego, CA, USA). Kolmogorov–Smirnov test were used to test the characteristics of participants' distribution. The data normally distributed were expressed as mean±SD, and the data with skewed distribution were shown as median (IQR, 25–75th). Independent samples *t*-test was used to compare the normally distributed variables, and Mann–Whitney *U* test was used to compare abnormally distributed variables. The Spearman's rank correlation coefficient analysis was performed to analyze the bivariate correlation between asprosin and other parameters. $p<0.05$ (two-sided) was considered as statistically significant.

RESULTS

The clinical characteristics of 170 subjects are described in Table 1. There were no significant differences in age, FSH, PRL, and TSH levels between the control and PCOS groups. PCOS patients had higher levels of different hormones and metabolic-associated parameters (i.e., LH, LH/FSH, E_2, T, AMH, fasting glucose, fasting insulin, HOMA-IR, DHEA-S, TC, HDL, LDL, and TG, p<0.05). Women in the PCOS group had significantly longer menstrual cycles than those in the control group (50.87±13.68 vs. 29.69±2.98; p<0.001). In the PCOS group, BMI was higher, and basal antral follicle numbers were more than in the control group (p<0.05).

As shown in Figure 1A, serum asprosin levels showed no significant difference between the PCOS and control groups [2.87 (2.18–4.47) vs. 3.24 (2.23–4.31) ng/mL, median (25–75th), p>0.05]. The asprosin levels were measured in different PCOS subtypes (Figures1B–D). The serum asprosin level in the PCOS HA group was notably lower than in the PCOS NHA group [2.52 (2.06–3.19) vs. 4.20 (2.35–5.79) ng/mL, median (25–75th), p<0.05] (Figure1B). The serum asprosin levels in the PCOS IR group were significantly lower than in the PCOS NIR group [2.46 (2.05–4.30) vs. 3.77 (2.47–7.18) ng/mL, median (25–75th), p<0.05] (Figure1C). In addition, this type of measurement was more pronounced in the PCOS IR&HA groups.

In the PCOS group, serum asprosin was negatively correlated with BMI, LH, T, basal antral follicles, fasting insulin, HOMA-IR, and TG. When adjusted for BMI, the correlations were not significant and asprosin was only positively correlated with PRL (r=0.426, p<0.001; Table 2). In addition, asprosin was still positively correlated with PRL (r=0.456, p=0.003) in PCOS NHA subjects. Moreover, there was no correlation between asprosin and other characteristics in PCOS HA subjects. These results indicate that obesity rather than PCOS might be responsible for the difference in asprosin levels.

Table 1. General clinical and laboratory characteristics of study participants.

	Total sample	Controls (n=77)	PCOS (n=93)	p-value
Age (years)[a]	28.48±3.47	28.34±3.06	28.60±3.78	0.615
BMI (kg/m²)[a]	23.75±4.10	22.30±3.69	24.95±4.05	<0.001
Menstrual cycles	41.33±14.79	50.87±13.68	29.69±2.98	<0.001
FSH (IU/L)[a]	6.15±1.51	6.32±1.13	6.02±1.76	0.183
LH (IU/L)[a]	7.84±4.54	5.55±1.63	9.74±5.26	<0.001
LH/FSH[a]	1.34±0.85	0.90±0.30	1.70±0.98	<0.001
E2 (pg/mL)[a]	40.87±17.70	35.03±12.80	45.71±19.70	<0.001
PRL (ng/mL)[a]	16.75±8.00	16.66±6.85	16.82±8.88	0.900
T (ng/dL)[b]	29.06 (22.27–62.84)	23.58 (18.06–28.67)	60.45 (27.82–68.35)	<0.001
TSH (μIU/mL)[a]	2.34±1.02	2.25±0.93	2.42±1.08	0.974
Basal antral follicles[a]	23.44±12.02	14.42±3.89	30.91±11.32	<0.001
AMH (ng/mL)[a]	7.85±4.96	5.52±3.21	10.12±5.32	<0.001
Fasting glucose (mmol/L) a	5.37±0.99	5.15±0.47	5.55±1.23	0.013
Fasting insulin (mIU/L)b	10.33 (7.38–18.97)	7.75 (6.35–10.20)	12.38 (8.76–25.30)	<0.001
HOMA-IR[b]	2.35 (1.71–4.81)	1.82 (1.49–2.27)	3.06 (2.12–6.62)	<0.001
DHEA-S (μg/dL)[a]	276.68±101.97	259.27±82.93	291.02±113.78	0.039
TC (mmol/L)[a]	4.47±0.85	4.29±0.87	4.61±0.82	0.023
HDL (mmol/L)[a]	1.35±0.28	1.43±0.24	1.29±0.30	0.004
LDL (mmol/L)[a]	3.01±0.72	2.80±0.70	3.17±0.70	0.002
TG (mmol/L)[b]	0.95 (0.68–1.33)	0.79 (0.63–1.09)	1.07 (0.81–1.45)	<0.001

BMI: body mass index; FSH: follicle stimulating hormone; LH: luteinizing hormone; E2: estradiol; PRL: prolactin; T: testosterone; TSH: thyroid-stimulating hormone; AMH: anti-Müllerian hormone; HOMA-IR: homeostasis model of assessment for insulin resistance index; DHEA-S: dehydroepiandrosterone sulfate; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides. [a]The data normally distributed are shown as mean ± SD. The independent sample *t*-test was performed. [b]The data distributed non-normally are shown as median (IQR, 25–75th). The Mann–Whitney *U* test was performed.

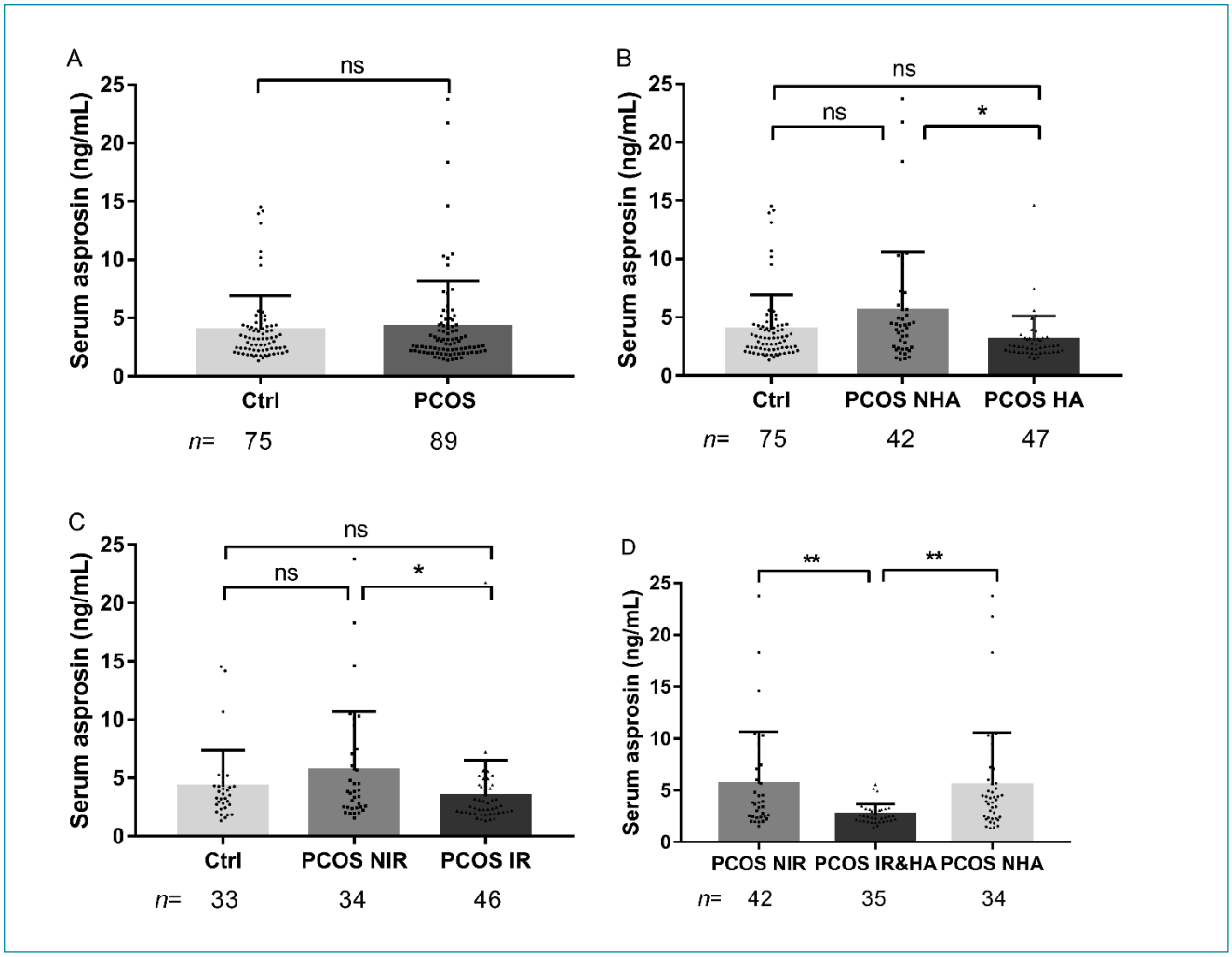

Figure 1. Serum asprosin levels between distinct groups. **(A)** Serum asprosin in PCOS group (n=89) had no statistically significant difference compared with the control group (n=75; p>0.05); **(B)** PCOS was subdivided into hyperandrogenism subtype (PCOS HA, n=47) and non-hyperandrogenism subtype (PCOS NHA, n=42), Serum asprosin in PCOS HA group were significantly lower than the PCOS NHA group (p<0.05); **(C)** PCOS patients were subdivided into insulin resistance subtype (PCOS IR, n=46) and non-insulin resistance subtype (PCOS NIR, n=34), Serum asprosin in PCOS IR group were significantly lower than the PCOS NIR group (p<0.05); **(D)** PCOS patients with both IR and HA (PCOS IR&HA, n=35). *indicates statistical significance at p<0.05 and **indicates statistical significance at p<0.01. PCOS: polycystic ovary syndrome.

DISCUSSION

This study showed that serum asprosin levels were similar between women in PCOS and control groups; however, lower levels were seen in PCOS HA and PCOS IR groups. Further analysis demonstrated that asprosin was positively correlated with PRL, i.e., independent of BMI.

Asprosin was first discovered by Romere et al. and was considered positively associated with IR[6]. Although IR was excluded from the diagnostic criteria for PCOS, it is a common physiological abnormality with metabolic dysfunctions in women with PCOS[14]. Adipose tissue can regulate the metabolism and balance the energy homeostasis through its role in endocrine regulation. Some small molecules secreted by the adipose tissue can either enhance or impair insulin action[15]. Recently, two other studies confirmed that asprosin was positively correlated with diabetes mellitus[8,16]. There are reports about the relationship between asprosin and PCOS; however, these results are inconsistent[10,17,18]. We would like to further explore the profiles of asprosin in PCOS subtypes.

We first compared the serum asprosin in women with PCOS and healthy controls in the concurrent period. Serum asprosin was comparable between women with or without PCOS, and it was slightly lower in the PCOS group. The PCOS group was then divided into different subgroups. Serum asprosin levels

Table 2. Bivariate correlations between serum asprosin level and other variables in the PCOS group and the subgroups categorized by testosterone.

	PCOS		PCOS (BMI-adjusted)		PCOS NHA (BMI-adjusted)		PCOS HA (BMI-adjusted)	
	r	p	r	p	r	p	r	p
Age (years)	0.111	0.299	0.039	0.717	0.015	0.924	0.147	0.329
BMI (kg/m^2)	-0.226	0.033	–	–	–	–	–	–
FSH (IU/L)	0.023	0.831	-0.006	0.952	0.021	0.895	-0.149	0.325
LH (IU/L)	-0.216	0.042	-0.164	0.127	0.054	0.739	-0.126	0.403
LH/FSH	-0.207	0.051	-0.137	0.204	0.010	0.952	-0.003	0.982
E2 (pg/mL)	-0.146	0.172	-0.048	0.654	0.153	0.341	-0.111	0.464
PRL (ng/mL)	0.170	0.110	0.426	<0.001	0.456	0.003	-0.058	0.704
T (ng/dL)	-0.299	0.004	-0.137	0.213	0.242	0.127	0.159	0.291
TSH (µIU/mL)	0.195	0.068	0.176	0.102	0.190	0.234	-0.083	0.582
Basal antral follicles	-0.255	0.016	-0.183	0.087	0.005	0.975	-0.080	0.596
AMH (ng/mL)	-0.207	0.079	-0.156	0.192	-0.099	0.545	0.012	0.948
Fasting glucose (mmol/L)	0.146	0.183	0.053	0.633	0.124	0.439	0.162	0.306
Fasting insulin (mIU/L)	-0.345	0.002	-0.195	0.083	-0.274	0.083	-0.070	0.677
HOMA-IR	-0.297	0.007	-0.158	0.164	-0.259	0.102	0.038	0.824
DHEA-S (µg/dL)	-0.072	0.505	0.016	0.885	0.148	0.361	0.252	0.094
TC (mmol/L)	-0.100	0.380	-0.075	0.514	-0.082	0.630	0.030	0.851
HDL (mmol/L)	0.209	0.062	0.189	0.093	0.180	0.287	0.142	0.371
LDL (mmol/L)	-0.144	0.199	-0.104	0.358	-0.135	0.425	0.063	0.691
TG (mmol/L)	-0.219	0.045	-0.075	0.499	0.036	0.826	-0.167	0.290

BMI: body mass index; FSH: follicle stimulating hormone; LH: luteinizing hormone; E2: estradiol; PRL: prolactin; T: testosterone; TSH: thyroid-stimulating hormone; AMH: anti-Müllerian hormone; HOMA-IR: homeostasis model of assessment for insulin resistance index; DHEA-S: dehydroepiandrosterone sulfate; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides. Correlations between variables were analyzed by using the Spearman's rank correlation coefficient analysis or the BMI-adjusted partial correlation test.

were lower in both PCOS HA and IR groups. We then analyzed the probable correlations between asprosin and PCOS. The results showed that asprosin was negatively correlated with IR and HOMA-IR, which contradicts earlier studies[6,8,16]. However, after adjusting for BMI, there was a positive correlation only between asprosin and PRL. Therefore, it is likely that obesity rather than PCOS might be responsible for the difference in asprosin levels. There might be some explanations for this. One possibility is that the serum asprosin might be influenced by confounding effects through sex hormones, specific population conditions, and repeated freeze-thaw cycles. Another possibility is the multiple interactions with some other adipokines such as irisin, visfatin, and adiponectin, which are also secreted by the WAT and associated with PCOS[19-21]. Meanwhile, we found that asprosin was positively correlated with PRL. Circulating PRL is mainly secreted by the lactotroph and mammosomatotroph cells in the pituitary gland. However, the adipose tissue can also produce PRL at extra-pituitary sites[22]. In both young healthy men and obese men, PRL was inversely associated with insulin sensitivity[23,24]. PRL produced by the adipose tissue was directly related to the PPARG, ADIPOQ, and GLUT4 levels in the human visceral and subcutaneous fat[24]. Considered together, PRL might influence asprosin levels through certain feedback mechanisms in women with PCOS, which also explains the first possibility.

Our study provides significant insights about the correlation between asprosin and PCOS. Three different studies about asprosin and PCOS were recently published[10,17,18]. Chia et al. reported that asprosin levels in women with PCOS were similar to those in corresponding controls[18]. However, Murat and Li found that circulating asprosin levels were elevated in women with PCOS compared with those in controls[10,17]. Our results were consistent

with the former results, but contrary to the latter. This diversity might be due to the different sample conditions and effects of PRL. Still, some limitations in this study should be acknowledged. For example, this study is based on EMR from a single hospital, and the sample size was relatively limited.

CONCLUSION

This study shows that women with PCOS HA or IR exhibit significantly lower levels of serum asprosin. The serum asprosin levels also correlated closely with various sex hormones and metabolic disorders, and the lower asprosin levels directly correlated with PRL levels.

AUTHORS' CONTRIBUTIONS

YJ: Data Curation, Project Administration, Validation, Writing – Original Draft. YL: Data Curation, Formal Analysis. ZY: Data Curation, Formal Analysis. PY: Data Curation, Formal Analysis. SZ: Funding Acquisition, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – Review & Editing.

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