Serum Asprosin Level in Different Subtypes of Polycystic Ovary Syndrome: A Cross-sectional Study

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Title Page

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

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23 **Abstract**

24 **Objective:** Polycystic ovary syndrome (PCOS) can be divided into different subtypes, including
25 insulin resistance (IR) and hyperandrogenism (HA). Asprosin is a novel hormone associated with IR;
26 however, the role of asprosin in women with PCOS has not been investigated. Thus, the aim of this
27 study was to investigate the relationship between serum asprosin levels and PCOS subtypes.

28 **Methods:** Ninety-three women with PCOS and 77 healthy women as controls were selected for this
29 study. Clinical and laboratory data were compared between the PCOS group and the control group.
30 The PCOS group was further divided into subgroups: 1) women with or without HA (PCOS HA and
31 PCOS NHA, respectively); 2) women with or without IR (PCOS IR and PCOS NIR, respectively).
32 Serum asprosin was measured by ELISA.

33 **Results:** Serum asprosin levels showed no significant difference between the PCOS and control
34 groups. However, it was significantly lower in the PCOS HA and IR groups compared to the
35 respective PCOS NHA and NIR groups ($P < .05$). In the PCOS group, serum asprosin was negatively
36 correlated with body mass index, luteinizing hormone, testosterone, basal antral follicles, fasting
37 insulin, Homeostatic Model Assessment of Insulin Resistance, and triglycerides. After adjusting for
38 BMI, the correlations were not significant and asprosin was only positively correlated with prolactin
39 ($r = 0.426$, $P < .001$).

40 **Conclusions:** Our study shows that women with PCOS HA or IR exhibit significantly lower serum
41 asprosin levels compared to controls, and the lower asprosin level directly correlated with PRL level.

42 **Keywords:** asprosin; PCOS; hyperandrogenism; insulin resistance

43

44 **Background**

Polycystic ovary syndrome (PCOS), also known as Stein-Leventhal syndrome, is a common and complex endocrine metabolic disease caused by genetic and environmental factors. The prevalence is 5 to 10% in women of reproductive age[1]. 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[2, 3]. PCOS increases the risk for type 2 diabetes mellitus (T2DM), gestational diabetes, and other pregnancy-related complications, cardiovascular events, and endometrial cancer[4]. IR is considered as the major risk factor for the onset of PCOS[5] and 70% of patients with PCOS have shown signs of IR[6].

Asprosin, a recently identified hormone, is secreted by the white adipose tissue (WAT) [7]. 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. Previous studies showed that asprosin was pathologically elevated in humans and mice with IR or obesity[7]. The olfactory receptor OLFR734 specifically binds with asprosin to modulate hepatic glucose production[8]. Several recent studies have shown that asprosin correlated with obesity in children and adults, T2DM and PCOS[9-16]. 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.

62

63 **Material and Methods**

64 **Study subjects**

The current study retrieved 170 serum samples, including 93 from the 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[17]: two of the following three criteria were positive, after the exclusion of other etiologies: 1) oligo and/or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, 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, or 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 (IVF) 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, $T > 60 \text{ ng/dL}$) and without HA (PCOS NHA); PCOS with IR (PCOS IR, $\text{HOMA-IR} \geq 2.5$) and without IR (PCOS NIR) [18, 19]. All the serum samples were collected in the follicular phase. Venous blood samples were collected in the morning after an overnight fasting period.

Clinical and laboratory data collection

Clinical and laboratory data were collected from electronic medical records (EMR) in our hospital. Anthropometric data included height, weight, body mass index (BMI), and menstrual cycle history. Serum hormones measured included follicle stimulating hormone (FSH), luteinizing hormone (LH),

89 estradiol (E2), prolactin (PRL), testosterone (T), thyroid-stimulating hormone (TSH),
90 dehydroepiandrosterone sulfate (DHEA-S), and anti-müllerian hormone (AMH); these were tested
91 using electrochemiluminescence. Basal antral follicles were counted between the third day and fifth
92 day of menstruation by vaginal ultrasonic examination. Metabolic related indicators including fasting
93 glucose, fasting insulin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-
94 density lipoprotein cholesterol (LDL-C), and triglycerides (TG) were measured. HOMA-IR was
95 calculated as fasting glucose (in mmol/L) * fasting insulin (in mIU/L) /22.5.

96 **Measurement of asprosin**

97 Serum asprosin was measured using a commercial human asprosin ELISA Kit (Catalog No:
98 E15190h, Wuhan EIAab Science Co. Ltd., China) according to the manufacturer's instructions. In
99 brief, 100 µL serum covered with the plate sealer was incubated at 37°C for 2 hours. The liquid was
100 then removed and 100 µL of detection reagent A was added and incubated at 37°C for 1 hour. Next,
101 the sample was washed 3 times and 100 µL detection reagent B was added. After 1-hour incubation,
102 the sample was washed 5 times and 90 µL of substrate solution was added. A 50 µL stop solution was
103 then added and 450 nm optical density was determined by automated microplate reader (PerkinElmer,
104 Inc., Waltham, MA, USA). Acquired data were calculated by CurveExpert 1.4 (Hyams D.G., Starkville,
105 MS.USA). The intra-assay coefficient of variation (CV) was $\leq 6.5\%$ and the inter-assay CV was $\leq$
106 9.8% .

107 **Statistical analysis**

108 All statistical analyses were conducted using SPSS software (IBM, Armonk, NY, version 21.0) and
109 GraphPad Prism 7 software (San Diego, CA, USA). Kolmogorov-Smimov test were used to test
110 characteristics of participants' distribution. Data normally distributed were expressed as mean $\pm$ SD

111 and data with skewed distribution were shown as median (IQR, 25th-75th). Independent samples t-
112 test was used to compare the normally distributed variables and Man-Whitney U test was used to
113 compare abnormally distributed variables. Spearman correlation analysis was performed to analyze
114 bivariate correlation between asprosin and other parameters. P value < .05 (two-sided) was
115 considered as statistically significant. The sample size power calculation was performed from an
116 online website (<http://powerandsamplesize.com/>). Considering the score between PCOS and control
117 subjects (power > 0.8; α = 0.05; sampling ratio = 2), 802 PCOS cases and 1604 control cases were
118 required. While considering the score between PCOS subtypes (power > 0.8; α = 0.05; sampling ratio
119 = 1), 41 PCOS HA cases and 56 PCOS IR cases were required.

120

121 **Results**

122 **Characteristics of the clinical subjects**

123 Clinical characteristics of the 170 subjects are described in Table 1. There were no significant
124 differences in age, FSH, PRL, and TSH levels between the control and PCOS groups. PCOS patients
125 had higher levels of different hormones and metabolic-associated parameters (LH, LH/FSH, E₂, T,
126 AMH, fasting glucose, fasting insulin, HOMA-IR, DHEA-S, TC, HDL, LDL, and TG, P < .05).
127 Women in the PCOS group had significantly longer menstrual cycles than those in the control group
128 (50.87 ± 13.68 vs 29.69 ± 2.98 ; P < .001). In the PCOS group, BMI was higher and basal antral
129 follicle numbers were more than in the control group (P < .05).

130 **Serum asprosin levels in distinct groups**

131 As shown in Fig.1A, serum asprosin levels showed no significant difference between the PCOS
132 and control groups [2.87 (2.18-4.47) vs. 3.24 (2.23-4.31) ng/mL, median(25th-75th), P > .05]. The

asprosin levels were measured in different PCOS subtypes (Supplementary Table1, Supplementary Table2 and Fig.1B-D). 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 (25th-75th), $P < .05$] (Fig.1B). 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 (25th-75th), $P < .05$] (Fig.1C). In addition, this trend was more pronounced in the PCOS HA & IR groups.

Correlation coefficient of variables associated with circulating asprosin

As listed in Table 2, Spearman analysis indicated that serum asprosin was positively correlated with TSH and HDL, and negatively correlated with BMI, fasting insulin, HOMA-IR, and TG in all the samples. However, after adjustment for BMI, asprosin was positively correlated only with PRL ($r = 0.399$, $P < .001$), TSH ($r = 0.162$, $P = .038$), and HDL ($r = 0.178$, $P = .033$). While 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 ($r = 0.426$, $P < .001$; Table 3). In addition, asprosin was still positively correlated with PRL ($r = 0.456$, $P = .003$) 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.

150

Discussion

The current 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, independent of BMI.

155 Asprosin was first discovered by Romere C et al. and was considered positively associated with
156 IR[7]. Although IR was excluded from the diagnostic criteria for PCOS, it is a common physiological
157 abnormality with metabolic dysfunctions in women with PCOS[20]. Adipose tissue can regulate the
158 metabolism and balance the energy homeostasis through its role in endocrine regulation. Some small
159 molecules secreted by the adipose tissue can either enhance or impair insulin action[21, 22]. Moreover,
160 Romere and his colleagues verified that asprosin level was higher in humans and mice with IR[7].
161 Recently, two other groups confirmed that asprosin was positively correlated with diabetes
162 mellitus[16, 23]. There have been reports about the relationship between asprosin and PCOS; however,
163 these results are inconsistent[13, 15, 24]. We would like to further explore the profiles of asprosin in
164 PCOS subtypes, and HA is one of the most important phenotypes of PCOS.

165 We first compared the serum asprosin in women with PCOS and healthy women in the concurrent
166 period. Serum asprosin was comparable between women with or without PCOS, and it was somewhat
167 lower in the PCOS group. The PCOS group was then divided into different subgroups. Serum asprosin
168 levels were lower in both, PCOS HA and IR groups, which was contrary to our expectations. We then
169 analyzed the probable correlations between asprosin and PCOS. The results showed that asprosin was
170 negatively correlated with IR and HOMA-IR, which contradicts previous studies[7, 16, 23]. However,
171 after adjusting for BMI, there was a positive correlation only between asprosin and PRL. Therefore,
172 it is likely that obesity rather than PCOS might be responsible for the difference in asprosin levels.
173 There might be some explanations for this. One possibility is that the serum asprosin might be
174 influenced by confounding effects through sex hormones, specific population conditions, and
175 repeated freeze-thaw cycles. Another possibility is the multiple interactions with some other
176 adipokines such as irusin, visfatin, and adiponectin, which are also secreted by the white adipose

177 tissue (WAT) and associated with PCOS[25-27]. Meanwhile, we found that asprosin was positively
178 correlated with PRL. Circulating PRL is mainly secreted by the lactotroph and mammosomatotroph
179 cells in the pituitary gland. However, the adipose tissue can also produce PRL at extra-pituitary
180 sites[28]. In both, young healthy men[29] and overweight or obese men[30], PRL was inversely
181 associated with insulin sensitivity. PRL produced by the adipose tissue was directly related to the
182 PPARG, ADIPOQ and GLUT4 levels in the human visceral and subcutaneous fat[30]. Considered
183 together, PRL might influence asprosin levels through certain feedback mechanisms in women with
184 PCOS, which also explains the first possibility. Moreover, elevated levels of insulin can stimulate
185 ovarian androgen production and cause elevated T by suppressing the sex-hormone binding globulin
186 (SHBG) [31]. We did not find any further correlations between asprosin levels and T after adjusting
187 for BMI. The specific mechanism might be beyond our cognition in this limited study and more in-
188 depth research is needed.

189 Our study provides significant insights about the correlation between asprosin and PCOS. Three
190 different studies about asprosin and PCOS were recently published[13, 15, 24]. Chia et al reported
191 that asprosin levels in women with PCOS were similar to those in corresponding controls[24].
192 However, Murat and Li found that circulating asprosin levels were elevated in women with PCOS
193 compared to those in controls[13, 15]. Our results were consistent with former, but contrary to the
194 latter. This diversity might be due to the different sample conditions and effects of PRL. Yet, some
195 limitations in this study should be acknowledged. For example, the study is based on EMR from a
196 single hospital and the sample size was relatively limited.

197 **Conclusions**

198 This study shows that women with PCOS HA or IR exhibit significantly lower levels of serum

199 asprosin. The serum asprosin levels also correlated closely with various sex hormones and
200 metabolic disorders, and the lower asprosin levels directly correlated with PRL levels. Our research
201 provides new clinical insights about the role of adipokines in the pathogenesis of PCOS.

202

203 **Acknowledgments**

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205 providing language polish services.

206 **Author contributions**

207 YH Jiang: data curation, project administration, validation, writing (original draft). Y Liu and ZH Yu:
208 serum sample collection, ELISA test performing. P Yang and L Xie: clinical data collection, data
209 analysis. XJ Shang: investigation, methodology, supervision, validation. SG Zhao: funding
210 acquisition, investigation, methodology, software, supervision, validation, visualization, writing
211 (review/editing).

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215 **Availability of data and materials**

216 All of the related results can be requested from the corresponding author.

217 **Ethics approval and consent to participate**

218 This study involving human serum samples and clinical data were approved by the ethics committee
219 of Center for Reproductive Medicine of Shandong University.

220 **Consent for publication**

221 Not applicable.

222 **Competing interests**

223 The authors declare that there is no conflict of interest regarding the publication of this paper.

224 **Acknowledgments**

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226 providing language polish services.

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325 **Figure Legends:**

326 Fig.1. Serum asprosin levels between distinct groups. (A) Serum asprosin in PCOS group (n=89) had
327 no significant statistically difference compared to the control group (n=75) [$P > 0.05$]. (B) PCOS was
328 subdivided into hyperandrogenism subtype (PCOS HA, n=47) and none-hyperandrogenism subtype
329 (PCOS NHA, n=42). Serum asprosin in PCOS HA group were significantly lower than the PCOS
330 NHA group ($P < 0.05$). (C) PCOS patients were subdivided into insulin resistance subtype (PCOS IR,
331 n=46) and none-insulin resistance subtype (PCOS NIR, n=34). Serum asprosin in PCOS IR group
332 were significantly lower than the PCOS NIR group ($P < 0.05$). (D) PCOS patients with both IR and
333 HA (PCOS IR&HA, n=35). * indicates statistical significance at $p < 0.05$ and ** indicates statistical
334 significance at $p < 0.01$.

335

336 **Additional files:**

337 **Supplementary Table 1 .docx**

338 General clinical and laboratory characteristics of PCOS NHA and PCOS HA subjects

339 **Supplementary Table 2 .docx**

340 General clinical and laboratory characteristics of PCOS NIR and PCOS IR subjects

Figures

Figure 1

Serum asprosin levels between distinct groups. (A) Serum asprosin in PCOS group (n=89) had no significant statistically difference compared to the control group (n=75) $P \geq 0.05$. (B) PCOS was subdivided into hyperandrogenism subtype (PCOS HA, n=47) and none-hyperandrogenism subtype (PCOS NHA, n=42). Serum asprosin in PCOS HA group were significantly lower than the PCOS NHA group ($P \leq 0.05$). (C) PCOS patients were subdivided into insulin resistance subtype (PCOS IR, n=46) and none-insulin resistance subtype (PCOS NIR, n=34). Serum asprosin in PCOS IR group were significantly lower than the PCOS NIR group ($P \leq 0.05$). (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 $p < 0.01$.

Supplementary Files

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