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Investigation of serum asprosin level in patients diagnosed of polycystic ovary syndrome in adolescent age

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Abstract

Polycystic ovary syndrome characterized by irregular menstruation, high serum androgen levels and infertility in the reproductive period. New markers are being studied to facilitate diagnosis. Asprosin is a peptide that is synthesized during fasting and stimulates glucose production from the liver. High levels of asprosin have been found to be associated with obesity, insulin resistance and diabetes. The aim is to answer the question 'Can serum asprosin level be used as a marker in the initial diagnosis of PCOS in adolescents without any disease?'. A total of 65 people between the ages of 12-18 who applied to the Antalya Training and Research Hospital Gynecology and Obstetrics Polyclinic between June 2020 and January 2021 were included in the study. The group was divided into two as 38 patients newly diagnosed with PCOS and 27 healthy control groups without any pathology. When the asprosin level of the cases diagnosed with PCOS and the cases in the control group were compared, it was observed that the asprosin level of the cases with PCOS was significantly higher (p=0.004). This study was a study showing that serum asprosin level can be used in the diagnosis of PCOS. It should be supported by other studies.

Keywords: PCOS, adolescent, asprosin, insulin resistance, hyperandrogenism

Introduction

Polycystic ovary syndrome characterized by irregular menstruation, high serum androgen levels and infertility in the reproductive period [1]. Changes in the hypothalamo-pituitary axis, LH hypersecretion, formation of abnormal oocytes due to increased ovarian folliculogenesis, steroidogenesis, and insulin secretion are thought to be effective in its pathophysiology [7]. While PCOS is present in 6-15% of women of reproductive age, it is seen in 6% of adolescents [2]. Polycystic ovary syndrome has short- and long-term consequences. Patients typically present with complaints of hirsutism and irregular menstrual cycles such as anovulation, amenorrhea, and oligomenorrhea. In many women of reproductive age, on the other hand, it is detected while investigating the causes of infertility. Long-term risks include unopposed estrogen-induced endometrial hyperplasia, endometrial cancer, non-insulin-dependent diabetes mellitus, cardiovascular diseases, dyslipidemia [2]. It is necessary to make a differential diagnosis of PCOS with other diseases in similar clinics. Rotterdam Criteria 2003 are used to facilitate diagnosis [3]. The diagnosis of polycystic ovary syndrome in adults was made by the presence of at least two of the Rotterdam criteria. [3]. However, there is no separate title for adolescents in the Rotterdam Criteria. In ESHRE 2018, the title of 'irregular cycles and ovulatory dysfunction' was created to distinguish between age-specific ovulation disorders and ovulatory disorders in adolescents [4]. Under the title of 'irregular cycles and ovulatory dysfunction' is located menstrual irregularities are normal in the first year after menarche, the cycle patterns should be between 21-45 days between 1-3 years after menarche, and not having a period longer than 90 days in any period after menarche [4]. The PCOM appearance on ultrasound is recommended to be used in the diagnosis 8 years after menarche [4]. In hyperandrogenism, acne, alopecia and hirsutism, which are not clinically known to be due to any other disease, should be considered. A modified Ferriman-Gallwey (mFG) score should be

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used for hirsutism and Ludwig score should be used for alopecia [4]. The markers to be used in biochemical evaluation are; free testosterone, free androgen index and bioactive testosterone [4].

New markers are being studied to facilitate diagnosis. Asprosin is a peptide that is synthesized during fasting and stimulates glucose production from the liver [5]. High levels of asprosin have been found to be associated with obesity, insulin resistance and diabetes [5]. Some studies have reported that insulin resistance and metabolic syndrome seen in PCOS are associated with asprosin [5-8]. It has been shown that asprosin levels in adult women with PCOS are higher than in healthy adult women [5].

In the diagnosis of PCOS, the patient's anamnesis, biochemical parameters and ultrasonographic image are used. Although anamnesis is an important branch, the cause of irregular menstruation in adolescent PCOS patients may be age-related, making the diagnosis difficult. Since PCOS is a collection of symptoms, the use of a single marker facilitates the diagnosis, since patients come with different complaints and examinations take time. There are no studies evaluating the level of asprosin in adolescents with PCOS. In this article, asprosin levels were evaluated in adolescents newly diagnosed with PCOS who had normal BMI and did not have metabolic diseases such as insulin resistance, DM, and hypo/hyperthyroidism. Asprosin level has been shown to be higher in adolescents with PCOS compared to the healthy group.

Materials and Methods

Ethics committee approval was obtained in Antalya Training and Research Hospital on 12/11/2020 with the decision numbered 17/10. A total of 65 people between the ages of 12-18, who applied to the department between June 2020 and January 2021, were included in the study after obtaining detailed consent from the patient's parents and himself.

38 patients newly diagnosed with PCOS constituted the study group and 27 healthy patients without any pathology constituted the control group. The patients were diagnosed in the presence of oligo/anovulation and hyperandrogenism, and ultrasound was not included in the diagnostic criteria. Thyroid disease, hyperprolactinemia, diseases causing adrenal hormone disorder, obesity, metabolic syndrome and insulin resistance were not included in the study. Oligomenorrhea (cycles longer than 45 days 1-3 years after menarche, cycles longer than 35 days 3 years after menarche) and chronic anovulation (absence of menstruation for more than 90 days in any period 1 year after menarche) were diagnosed according to ESHRE 2018. Hirsutism and acne complaints were accepted as clinical determinants of hyperandrogenism. The modified Ferriman Gallwey scoring system became our predictor for the diagnosis of hirsutism. The hair density of a total of nine anatomical regions was scored between 0-4 points, and those with a total score of 8 and above were diagnosed with hirsutism. The ESHRE 2018 criteria recommend that ultrasound not be used as a diagnostic criterion for the first 8 years after menarche in adolescents. Ultrasound was not used as a diagnostic criterion in our study. Detailed anamnesis was taken from all cases; Age, body mass index (BMI), gravida, parity, family history, comorbidity, family history, smoking and alcohol use, weight / height ratios were calculated.

If oligo/anovulation was detected in newly diagnosed PCOS cases who did not use any medical treatment, samples were taken from 2 biochemistry tubes in the morning fasting at the first application. Venous blood samples were taken from the patients in 2 biochemistry tubes, on the 2nd-5th days of the menstruation for those with regular menstruation and on the morning of the examination day for those with chronic anovulation. After centrifugation at 4000 rpm for 10 minutes, the sera were transferred to Eppendorf tubes and stored under suitable conditions (-80 °C) for the asprosin study until the study day.

The serum asprosin level was studied with a commercially available elisa kit (AFG Bioscience, USA, catalog no: EK715241).

Statistical Data

SPSS 18.0 (Statistical Package for Social Sciences) system was used to evaluate the data. Normal distribution was evaluated with the Kolmogorov-Smirnov test. Student t-test was used for the variables with normal distribution between the two groups, and Mann Whitney U test was used for those without normal distribution. Categorical data were compared with the chi-square test. Values in both groups were presented as "mean ± standard deviation". P value <0.05 was considered significant.

Results

This study was conducted on a total of 65 cases, 38 (58.4%) PCOS and 27 (41.5%) control group, aged 12-18 between February 2020-2021. No significant difference was observed in the calculations of weight, BMI, waist circumference, hip circumference and waist/hip ratio ($p>0.05$). In hirsutism, a significant difference was observed as 16.6±5.5 in patients with PCOS and 7.5±2.9 in the control group ($p<0.001$) (Table 1).

In the study, no significant difference was observed in values such as FSH, estradiol, 17-OH progesterone, TSH, and prolactin ($p>0.05$) (Table 2). LH value was significantly higher in PCOS patients (15.4±8.6 mIU/mL in PCOS group, 11.1±8.8 mIU/mL in control group; $p=0.015$) (Table 2). When serum androgen values are compared, there is a significant difference between total testosterone (median values PCOS group 0.68 ng/mL, control group 0.5 ng/mL; $p=0.00$), SHBG (PCOS group 40.1±32.3 nmol/L, control group 51.1±21.6; $p=0.002$), SAI (PCOS group 6.7±4.8, control group 3.2±1.4; $p<0.001$) values (Table 2). No significant difference was observed in free testosterone and DHEAS levels ($p>0.05$) (Table 2).

No significant difference was observed in the fasting glucose, fasting insulin, HbA1c, HOMA-IR and QUICKI indices in which insulin sensitivity was investigated. LDL values differ significantly when looking at lipid values (105.5±32.4 in the PCOS group, 90.9±24.2 in the control group; $p=0.038$) (Table 2). There was no significant difference in total cholesterol, triglyceride and HDL values ($p>0.05$) (Table 2).

As a result of the study, we found a difference in asprosin levels between the PCOS group and the control group (PCOS group 191.8±107.1, control group 144.3±39.8; $p=0.004$) (Table 2).

Table 1. Demographic data of PCOS and control groups

	Control groups (n=27)	PCOS groups (n=38)	p value
Age	16.4±1.5	16.3±1.8	0.84
Size (cm)	161.5(150-173)	160(136-177)	
Kilo (kg)	61.8±12.3	57.5±9.6	0.13
BMI (kg / m²)	23.4±4.2	22.3±3.5	0.25
Waist circumference (cm)	78(60-93)	75(48-98)	0.2
Hip circumference (cm	94.5(79-110)	95(60-118)	0.25
Waist/hip	0.83±0.07	0.79±0.06	0.08
Hirsutism score	7.5±2.9	16.6±5.5	001*

Data are expressed as mean ± standard deviation or median (minimum-maximum) value. BMI: Body Mass Index
* Statistically significant difference

Table 2. Laboratory results of PCOS and control groups

	Control group (n=27)	PCOS group (n=38)	p value
Hormone values			
FSH (mIU/mL	5.7±2.4	6.8±2.5	0.094
LH (mIU/mL	11.1±8.8	15.4±8.6	0.015*
Estradiol (ng/L)	71.1±42.7	62.9±49.6	0.226
17-OHP (ng/mL	1.5±0.8	1.5±1.1	0.734
TSH (uIU/mL	.1±0.9	2.1±1.1	0.679
Prolactin (µg/L)	17.1±10.6	15.1±6.3	0.947
Androgen values			
Total testosterone (µg/mL)	0.5(0.2-0.88)	0.68(0.17-1.12)	0.007
Free testosterone (ng/L)	2.1±1.4	2.2±1.3	0.989
DHEAS (µg/L)	222.9±104.8	244.7±118.3	0.627
SHBG (nmol/L)	51.1±21.6	40.1±32.3	0.002*
Free androgen index	3.2±1.4	6.7±4.8	<0.001*
Insulin sensitivity and glucose values			
Fasting insulin (uIU/mL)	8.2±4.6	9.3±5.1	0.293
Fasting glucose (mg/dL)	85.1±9.6	85.6±10.8	0.562
HbA1c	5.1±0.3	5.1±0.6	0.867
HOMA-IR	1.8±1.1	2.1±1.2	0.42
QUICKI	0.35(0.3-0.4	0.35(0.29-0.45)	0.405
Lipid values			
Triglyceride (mg/dL)	102.7±65.7	106.6±47.7	0.1
Total cholesterol (mg/dL)	167.5±30.8	181.9±33.6	0.08
HDL cholesterol (mg/dL)	53(40-73)	56(39-84)	0.368
LDL cholesterol (mg/dL)	90.9±24.2	105.5±32.4	0.038*
Asprosin	144.3±39.8	191.8±107.1	0.004*

Data are expressed as mean ± standard deviation or median (minimum-maximum) value. PCOS, polycystic ovary syndrome; FSH, follicle-stimulating hormone; LH, luteinizing hormone; 17-OHP, 17-hydroxyprogesterone; TSH, thyroid-stimulating hormone; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone binding globulin; HOMA-IR, homeostasis model assessment insulin resistance; QUICKI, quantitative insulin-sensitivity check index; HDL, high-density lipoprotein; LDL, low-density lipoprotein

Table 3. Correlation analysis of asprosin level with clinical parameters in control and PCOS groups

	Control		PCOS	
	r	Value	r	p value
Age	0.031	0.878	0.121	0.468
Size	-0.284	0.151	-0.314	0.055
Weight	0.173	0.389	0.296	0.071
BMI	0.197	0.235	0.504	0.007*
Waist circumference	0.081	0.63	0.513	0.006
Hip circumference	0.065	0.7	0.403	0.037
Waist/hip	0.236	0.154	0.39	0.044*
Hirsutism score	0.016	0.937	0.091	0.587

PCOS, polycystic ovary syndrome; BM, Body Mass Index *S1tatistically significant difference

Table 4. Correlation analysis of asprosin level with biochemical parameters in control and PCOS groups

	Control		PCOS	
	r	Value	r	Value
FSH	-0.137	0.496	-0.9	0.593
LH	0.145	0.47	0.007	0.967
Estradiol	0.105	0.601	0.153	0.358
TSH	0.079	0.696	0.186	0.264
Prolactin	-0.216	0.28	-0.121	0.47
17-OHP	-0.309	0.116	0.027	0.872
DHEAS	0.001	0.995	0.069	0.679
SHBG	0.303	0.125	0.089	0.597
Total testosterone	0.26	0.19	-0.009	0.957
Serbest testosterone	-0.013	0.948	-0.189	0.255
Free androjen indeksi	-0.172	0.39	-0.105	0.529
Fasting insulin	0.249	0.21	0.052	0.758
Fasting glucose	0.156	0.436	0.117	.486
HbA1c	0.225	0.258	0.113	0.94
HOMA-IR	0.11	0.585	0.116	0.486
QUICKI	-0.241	0.227	-0.049	0.769
Total colesterol	-0.024	0.904	0.042	0.8
Triglyceride	0.32	0.104	0.201	0.228
HDL colesterol	-0.272	0.17	-0.259	0.116
LDL colesterol	0.038	0.85	0.00	0.99

PCOS, polycystic ovary syndrome; FSH, follicle-stimulating hormone; LH, luteinizing hormone; 17-OHP, 17-hydroxyprogesterone; TSH, thyroid-stimulating hormone; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone binding globulin; HOMA-IR, homeostasis model assessment insulin resistance; QUICKI, quantitative insulin-sensitivity check index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Discussion

Polycystic ovary syndrome is an endocrinological disorder with short-term comorbidities such as oligo/anovulation, hirsutism, and insulin resistance, and long-term comorbidities such as infertility, metabolic syndrome, oxidative stress and cardiovascular diseases [1,9]. The diagnosis includes chronic anovulation, clinical or biochemical hyperandrogenism findings and PCOM appearance on ultrasound according to the Rotterdam 2003 criteria [3]. The presence of two-thirds of these criteria allows for diagnosis in adults [3]. There was no consensus on the use of these diagnostic criteria in adolescents. The guideline 'Evidence-based assessment and management of polycystic ovarian syndrome' was updated by ESHRE in 2018 [4]. In the guide, the title of 'irregular cycles and ovulation disorders' has been created for adolescents [4]. In our study, adolescents were diagnosed with PCOS according to the criteria under this title.

Asprosin stimulates glucose release from the liver during the fasting period [10]. High levels of aspronin have been associated

with insulin resistance, obesity, DM and metabolic syndrome [5,6]. In a study, regardless of PCOS and Type 2 DM, the asprosin level in overweight/obese individuals was shown to be significantly higher than in thin individuals [6]. Similar results were found in studies conducted with children and adolescents.

Asprosin level in obese children was observed to be higher than in normal weight children [11]. In one study, the serum asprosin level in obese girls was found to be higher than obese boys [12]. In other studies conducted with children and adolescents, no difference was observed between asprosin level and gender. In our study, we excluded adolescents with obesity and diseases such as glucose intolerance, DM, hypo/hyperthyroidism, and obesity, as we did not want the asprosin level to be affected by any endocrinological disease. In our study, when the waist circumference of 19 patients was evaluated according to the percentile card for age, it was found to be over 90%. Although a significant difference was observed in LDL values in cases diagnosed with PCOS in our study [p=0.038); no difference was observed in total cholesterol, triglyceride and HDL levels. High LDL alone is not enough to diagnose metabolic syndrome in children [13,14].

Some studies suggest that waist circumference alone may be a better indicator of body fat [15]. In our study, while the mean waist circumference of the PCOS group was 75 cm, the mean waist circumference of the control group was 78 cm and no significant difference was observed (p=0.2) (Table 1). A waist/hip ratio >0.85 makes the diagnosis of android type obesity [16]. When the waist/hip ratio was evaluated in our study, the mean was 0.79±0.06 in the PCOS group and 0.83±0.07 in the control group, and no significant difference was observed (p=0.08) (Table 1). Android type obesity is a significant risk for the development of systemic diseases such as cardiovascular diseases and type 2 diabetes in the future [15]. In studies, obesity rates were found to be higher in adult patients diagnosed with PCOS than in the control group [15,17]. In our study, BMI was found to be 22.3±3.5 in the PCOS group and 23.4±4.2 in the control group, and no significant difference was found (p=0.25) (Table 1).

Insulin resistance and hyperinsulinemia are seen in patients with PCOS. The etiology of insulin resistance present in patients with PCOS has not been fully elucidated.

To evaluate insulin resistance, fasting glucose, fasting insulin, HbA1c, HOMA-IR, QUICKI index, which were studied from serum biochemistry, were used. Fasting blood glucose <110 mg/dL is accepted as normal in most literature [13,14]. Patients with fasting glucose >110 mg/dL are diagnosed with impaired fasting glucose [13,14]. The reference value for fasting glucose in our hospital laboratory is 106 mg/dL, and no significant difference was observed between the groups in our study. Diabetes mellitus can be excluded in cases with an HbA1c value below 5.7% [17]. In our study, the HbA1c levels of the cases were <5.7, and no significant difference was observed between the PCOS patients and the control group. The higher the HOMA index value, the greater the insulin resistance [18]. Although different reference values are taken in various studies, it is stated that values above 2.4-2.7 indicate insulin resistance in the Turkish population [19]. In the study of Keskin et al., the reference value of the HOMA index value for adolescents was stated as 3.16 [20]. In our hospital, the reference value for the HOMA index was calculated as 2.5. When analyzed according to this value, no significant difference was observed between the groups in terms of HOMA index.

In studies on the QUICKI index, it has been found that glucose intolerance, insulin resistance, diabetes, hyperlipidemia, and disorders that are a combination of these metabolic disorders are more common in people with a low index value than in healthy individuals [21]. Evaluation of QUICKI index results for adolescents is the same as for adults. QUICKI index of <0.339 indicates insulin resistance [21]. In our study, a significant difference was not observed in the QUICKI index PCOS and control groups.

There is an increased LH response to GnRH in PCOS [22]. In addition, hyperinsulinism causes increased LH secretion and increased free androgen levels and decreased SHBG levels [22]. In our study, in adolescents diagnosed with PCOS, LH (p=0.015) and total testosterone (p=0.007) levels were found to be significantly higher than the control group, and SHBG (p=0.002) levels to be significantly lower.

Studies have shown that asprosin and SHBG levels are negatively correlated [6]. In our study, however, no significant results were observed between SHBG in the correlation analysis performed with asprosin (Table 3).

Free testosterone is responsible for most of the clinical manifestations of hyperandrogenemia. For the diagnosis of hyperandrogenemic disorders, the evaluation of free testosterone level seems to be more sensitive than the evaluation of total testosterone level [23]. Serum DHEAS levels indicate adrenal-induced elevation of androgen levels [23]. In our study, no significant difference was observed in serum free testosterone and DHEAS levels in PCOS and control groups. The free androgen index is an index used to calculate the amount of biologically active testosterone [24]. It is a ratio that has been shown to be of clinical importance in determining high androgen values in serum [24]. Studies have found that the free androgen index is higher in patients with PCOS [25]. In our study, SAI value was found to be significantly higher in PCOS patients compared to the control group (p<0.001). The clinical evaluation of hirsutism was done with a modified Ferriman-Gallwey [4]. In our study, the results of hirsutism scoring based on mFG scoring were also significantly higher in patients with PCOS than in the control group (p<0.001) (Table 1).

Asprosin is a protein whose synthesis increases with fasting. It provides glucose release from the liver to the blood [5]. The amount of asprosin that rises with hunger decreases with nutrition. In addition, in case of hyperlipidemia, asprosin is secreted from β cells [26]. High levels of asprosin have been associated with obesity, insulin resistance, type 2 DM, and hyperlipidemia. In some studies, it has been mentioned that the insulin resistance seen in patients with PCOS may be caused by asprosin [27]. In another study, it was mentioned that asprosin levels and insulin resistance, BMI, HOMA-IR and SAI were positively correlated [28].

We included adolescents who did not have any endocrinological diseases such as insulin resistance, hypothyroidism, hyperlipidemia. In addition, patients with insulin resistance, hyperlipidemia or metabolic syndrome in their serum biochemistry were excluded from the study.

In studies conducted on women with adult PCOS, asprosin levels

were found to be higher than the control group [28].

Studies were performed with blood values taken from both the patient group and the control group in the follicular phase. In our study, the blood values of our patients who applied to the outpatient clinic were determined on the 2nd-3rd day of the menstrual cycle or if there is chronic anovulation (absence of menstruation for 3 months or more) on the day of admission. In our results, when the asprosin level of the cases diagnosed with PCOS and the cases in the control group were compared, it was seen that the asprosin level of the cases with PCOS was significantly higher (p=0.004).

Conclusion

It is difficult to diagnose PCOS in adolescents and to distinguish whether it is due to age-specific ovulatory irregularity or ovulatory dysfunction. Can asprosin be used as a diagnostic marker in the diagnosis of adolescent PCOS patients? due to the difficulty in making the first diagnosis in adolescence this study was conducted to answer the question. Considering that asprosin may be affected by endocrinological diseases such as obesity, DM, insulin resistance and metabolic syndrome, this group was excluded from the study. As a result of the study, it was shown that the level of asprosin was high in an adolescent diagnosed with PCOS. In the light of this study and if larger studies to be conducted in the future show similar results, it may be important to measure the level of asprosin in the blood in making the first diagnosis in adolescent PCOS.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Ethics committee approval was obtained in Antalya Training and Research Hospital on 12/11/2020 with the decision numbered 17/10.

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