GUHES 2024; 6 (3): 107-116
DOI: 10.59124/guhes.1604306

Research Article

Journal of Gazi University Health Sciences Institute

journal homepage*:* https://dergipark.org.tr/tr/pub/guhes

Serum Adipsin Levels in Obese and Normal Weight Adolescents with Polycystic Ovary Syndrome

Sevgi Yardım Akaydın[1], Çağla Emiral[1], Ayşe Derya Buluş[2], Yüksel Yaşartekin[2]

[1]Gazi University, Faculty of Pharmacy, Department of Biochemistry, Ankara, Türkiye
[2]University of Health and Sciences, Department of Pediatric Endocrinology, Kecioren Training and Research Hospital, Ankara, Türkiye

Article info:

Received: 20.12.2024

Accepted: 25.12.2024

Keywords:

adipsin,
adolescent PCOS,
obesity

Abstract

Polycystic ovary syndrome (PCOS) is a chronic and heterogeneous disease associated with obesity, hyperinsulinemia, dyslipidemia and chronic low-grade inflammation. Adipsin is a protein that is mostly secreted from adipose tissue and is a structural homolog of complement factor D, the rate-limiting enzyme of the alternative complement system. The aim of this study was to investigate adipsin levels in adolescents with PCOS and their relationship with obesity. 40 normal weight--children with PCOS and 40 obese-children with PCOS, and 40 normal weight healthy children participated in our study. Adipsin levels of adolescents in each group was measured in morning fasting blood samples by a commercial ELISA kit. Adipsin levels showed statistically significant differences between the groups ($p<0.001$). Normal-weight PCOS adolescents had higher adipsin levels than both obese PCOS and healthy controls. A negative correlation was observed between adipsin levels and BMI in the PCOS group ($r=-0,457$, $p<0,001$). In conclusion, adipsin can be considered as an independent risk factor in normal weight PCOS adolescents and may help in the diagnosis of PCOS in normal weight children with other symptoms.

Sevgi Yardım Akaydın **(Corresponding author);** ORCID: 0000-0002-0927 5188, e-mail: sevgiy@gazi.edu.tr
Çağla Emiral; ORCID: 0000-0002-5185-9849, e-mail: caglaemiral@gmail.com
Ayşe Derya Buluş; ORCID: 0000-0003-2865-4420, e-mail: drderyabulus@hotmail.com
Yüksel Yaşartekin; ORCID: 0000 0002 5620 8199, e-mail: yukselyurdugul@gmail.com

Citation: Akaydın, Y. S., Demiral, Ç., Buluş, D.A., & Yaşartekin, Y. (2024). Serum adipsin levels in obese and normal weight adolescents with polycystic ovary syndrome. *Journal of Gazi University Health Sciences Institute*, 6(3), 107-116. https://doi.org/10.59124/guhes.1604306

1. Introduction

Polycystic ovary syndrome (PCOS) is considered a chronic and heterogeneous disorder that usually manifests itself during adolescence and is seen in approximately 10-20% of adolescent and young adult women worldwide (Salhah et al., 2024; Siddiqui et al., 2022). PCOS is a condition characterized by the formation of cysts in the ovarian follicles as a result of hormonal changes and imbalances. The diagnosis of PCOS is based on the presence of multiple cysts in the ovary, and as the number of cysts increases, the condition of "polycystic ovary" (multi-cystic ovaries) occurs (Patel, 2018; Yang and Chen, 2024).

The pathogenesis of PCOS involves a complex interaction of genetic and environmental factors such as chemical exposure (Patel, 2018). Various hormone derangements are also seen in PCOS. Cycle duration and ultrasound (follicle count, mean ovarian volume) parameters, glucose tolerance test (GTT), prolactin test, endocrine and lipid profiles may indicate PCOS (Tsutsumi and Webster, 2009). However, insulin and congenital adrenal hyperplasia may direct the pathogenesis of PCOS. Abnormal course of androgen and estrogen hormones results in metabolic disorders such as overweight and obesity, diabetes, insulin resistance and hyperinsulinemia, infertility and disrupted menstrual cycle in PCOS patients (Chang et al., 2024; Patel, 2018; Yang & Chen, 2024). Cardiovascular diseases, psychological disorders, dyslipidemia, infertility and cancer are also associated with PCOS (Patel, 2018; Siddiqui et al., 2022). These pathophysiologies associated with PCOS are also associated with each other (Siddiqui et al., 2022).

DNA damage due to oxidative stress has been shown to be associated with ovarian carcinoma in women with PCOS (Siddiqui et al., 2022).

Some steps regarding the origins of the development of adolescent PCOS have been revealed. Decreased weight gain in the late prenatal period and increased weight gain in the early postnatal period create an imbalance between early subcutaneous fat formation and subsequent lipogenesis processes (Ibáñez & de Zegher, 2023). In particular, when sufficient lipid storage capacity is not developed in the early period, the body's increased lipid storage needs cannot be met, and this creates metabolic stress. In the second step, it is noteworthy that the body develops a response to ectopic fat in late childhood. In this process, the hormone dehydroepiandrosterone sulfate, whose levels increase in circulation, plays a role in the early onset and acceleration of pubertal processes, accelerating the maturation of girls. Activation of the gonadotropic axis accelerates sexual maturation, while changes in the thyroid axis increase metabolic rate and accelerate growth. All of these hormonal changes act as an adaptive response of the body to ectopic fat accumulation, resulting in accelerated growth and maturation. The third step is the cessation of growth in height as epiphyseal fusion occurs in the growth plates, and the effects of the body's adaptive response to ectopic fat by accelerating growth decrease. With the cessation of growth, the body's energy expenditure decreases, which may cause the excess energy to be stored as more ectopic fat.

During this process, the effects of the increase in levels of hormones such as LH, TSH, DHEAS and testosterone observed in the previous stages decrease, and these hormones tend to return to normal levels.

Adipose tissue has been described as an endocrine and inflammatory organ that secretes adipokines that affect systemic metabolism, stores energy, and secretes them when needed (Byeon et al., 2023; Scherer, 2019). Adipsin is an important adipokine secreted by adipocytes and is a protein that has an effect on the function of adipose tissue and cardiometabolic processes (Milek et al., 2022). Adipsin, first identified as *complement factor D* in 1987, is an enzyme belonging to the serine protease family and is expressed in both adipose cells and nervous system cells (Cook, 1985). Since adipsin is a protein produced by adipose tissue and released into circulation, it plays an important role in the homeostasis and energy metabolism of adipose tissue (Dare & Chen, 2024; Flier et al., 1987; Lo et al., 2014). Human studies have shown positive correlations between adipsin serum concentrations and BMI (Milek, 2022). The fact that adipsin levels are associated with age, body weight, body mass index (BMI), fasting plasma glucose, and leptin emphasizes the importance of adipsin in the pathophysiology of obesity, insulin resistance, and diabetes (Milek et al., 2022). High adipsin levels in prediabetic individuals suggest that adipsin can be used as a possible biomarker during this process when glucose metabolism deteriorations begin. This finding suggests that it may be important to monitor adipsin not only in individuals with Type 2 diabetes but also in prediabetic individuals at risk of developing diabetes.

High adipsin levels may be an indicator of early metabolic deteriorations such as inflammation, insulin resistance, and energy imbalance, and thus may provide better predictions about the risk of developing diabetes in patients with impaired glucose tolerance.

There are a few studies examining serum adipsin levels in women with PCOS. Our study will be the first study evaluaing adipsin levels in children diagnosed with PCOS during adolescence.

2. Materials and Methods

2.1. Study groups

The study included 40 over-weight adolescent with PCOS and 40 normal-weight adolescent with PCOS between the ages of 10-20 who applied to the Pediatric Endocrinology Polyclinic of Keçiören Training and Research Hospital (KAEH) and 40 healthy and normal weight female adolescent who applied to the Healthy Child Polyclinic.None of the controlsubjects or the PCOS patients had clinical or laboratory evidence of any disease that might have affected the parameters to be measured. The demographic parameters and laboratory results of PCOS patients and healthy controls are given in Table 1. The study was approved by the Ethical Committe of Gazi University Local ethics committee (dated 12.09.2022, ref.no:685). All the subjects were recruited on a voluntary basis. Children and their families were informed verbally and in writing about the details of the study before they were included in the study. Along with that, consent was obtained from both parents and children by signing an informed consent form. Hyperandrogenism, oligomenorrhea or amenorrhea associated with chronic anovulation, and polycystic

ovarian morphology are classic features of PCOS (Dumesic et al., 2015). The current consensus is that the Rotterdam criteria are appropriate for adult women. Women must meet two of three characteristics for a diagnosis of PCOS: oligo-ovulation or anovulation, clinical and/or biochemical hyperandrogenism, or polycystic ovarian morphology on ultrasound after exclusion of other disorders. However, it is difficult to define appropriate diagnostic criteria for PCOS in adolescent girls because irregular menstruation, cystic acne, mild hyperandrogenism, and multifollicular ovarian morphology, which can be seen in PCOS, can also occur during normal pubertal maturation, making the diagnosis of PCOS in adolescent girls difficult (Ib´añez et al., 2017; Teede et al., 2018; Witchel et al., 2015). Similar to the evaluation of adult women, disorders such as CAH associated with irregular menstruation and/or hyperandrogenism, typically nonclassical 21-hydroxylase deficiency, androgen-secreting tumors, thyroid dysfunction, hyperprolactinemia, Cushing's syndrome, exogenous use of steroid hormones/androgens, or severe IR syndrome need to be excluded. Patients who met the criteria after these exclusions were included in the PCOS group.

In children, instead of fixed BMI values as in adults, percentile curves prepared according to age and gender are used. Since there may be differences between ethnic groups, each country should use percentile curves prepared for its own children. Although BMI normograms prepared by the CDC (The Centers for Disease Control and Prevention) are available in the USA, BMI percentile values prepared by Olcay Neyzi and his colleagues are used for this purpose in our country (Neyzi et al, 2015).

A BMI below the 5th percentile for age and gender is defined as “underweight”, between the 5th and 85th percentile is defined as “normal weight”, between the 85th and 95th percentile is defined as “overweight”, above the 95th percentile is defined as “obese”, and above 120% of the 95th percentile value or a BMI of ≥35 kg/m^2 (whichever is lower) is defined as “severe obesity” (Kelly et al, 2013; Skinner et al, 2018). When classifying according to the standard deviation score (SDS), according to gender and age, if the BMI SDS is between -1 and 1, it is considered as "normal weight"; if it is between 1 and 2, it is considered as "overweight" and if it is ≥2, it is considered as "obese" (Flegal et al, 2009; Gulati et al, 2012).

Blood samples were taken from the children participating in the study after at least 8 hours fasting. The blood sample was centrifuged and the serum part was separated and stored at -20°C.

2.2. Experimental Measurements

The amounts of serum adipsin (Human ELISA kits, Elabscience, China) were determined with a commercial kit. In addition, all children's fasting blood triglyceride (TG), total cholesterol (TC), LDL-C, HDL-C, E2, LH, FSH, CRP, and insulin measurements were also made with routine laboratory tests.

2.3. Statistical analysis

The data obtained as a result of the study are indicated as the mean (standard deviation). Data analysis was

performed using IBM SPSS Statistics 22.0 software (IBM Corporation, Armonk, NY, USA). Whether the distributions of continuous variables were normal or not was determined by Kolmogorov-Smirnov test. Chi-square test was used for comparison of qualitative data in comparison of demographic data. The distribution of the variables was not normal so significance of differences between medians were estimated by Kruskal Wallis test for more than two independent groups. Spearman's rank correlation coefficient (r) was used to examine relationships between parameters. A P value <0.05 was considered significant.

3. Results

In the Kolmogorov-Smirnov test (significance level was taken as 0.05), the levels of laboratory parameters in our study did not show a normal distribution. For this reason, non-parametric tests were applied in the statistical analysis of the findings.

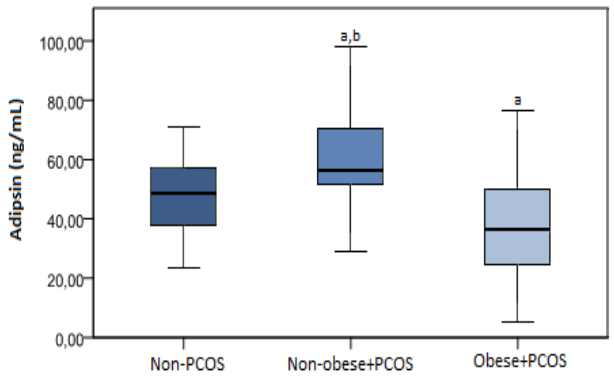
The study group was divided into 3 groups: over-weight adolescents with PCOS (obese+PCOS, n=40), normal-weight adolescents with PCOS (non-obese+PCOS n=40), and healthy controls of the same age group who did not have PCOS or any other disease (non-PCOS, n=40). The study groups were compared statistically according to age, BMI, family obesity status and family PCOS history, and the difference between some criteria was found statistically significant ($p<0.05$) (Table I). Also, HDL-Cholesterol, triglyceride, E2, FSH, LH, CRP and insulin levels showed a significant difference between groups ($p<0.05$) (Table I).

Table 1. Main characteristics of adolescents with PCOS and normal weight healthy controls

Variable	Obese + PCOS (N= 40)	Non-obese + PCOS (N= 40)	Non-PCOS (N=40)	P
Age, Mean (Standard Deviation)	15.5 (1.2)	14.8 (2.0)	14.5 (2.0)	0.046
BMI, Mean (Standard Deviation)	32.6 (4.4)	21.5 (3.0)	21.7 (3.8)	**0.001**
Family history of PCOS				
Yes, N (%)	8 (20.5)	10 (25)	1 (2.5)	**0.015**
No, N (%)	31 (79.5)	30 (75)	39 (97.5)	
Obesity status of the family				
Yes, N (%)	19 (47.5)	7 (17.5)	5 (12.5)	**0.001**
No, N (%)	21 (52.5)	33 (82.5)	35 (87.5)	
Laboratory Parameters				
Total Cholesterol (mg/dL)	161.2 (31.7)	176.4 (39.5)	164.5 (23.1)	0.235
LDL- Cholesterol (mg/dL)	91.3 (23.3)	101.6 (29.2)	101.5 (25.0)	0.216
HDL- Cholesterol (mg/dL)	45.9 (10.4)	50.8 (11.0)	50.5 (11.6)	**0.002**
Triglyceride, mg/dL	152.5 (112.8)	100.1 (46.5)	106.0 (47.8)	**0.020**
E2, pg/mL	60.6 (23.8)	81.8 (27.6)	109.5 (58.3)	**0.001**
FSH, mIU/mL	6.2 (3.1)	3.4 (3.9)	4.1 (2.1)	**0.001**
LH, IU/L	2.1 (1.7)	3.0 (3.2)	1.9 (1.1)	0.357
CRP, mg/dL	7.7 (2.0)	3.5 (2.3)	2.4 (3.0)	**0.001**
Insulin, mU/L	33.3 (30.8)	17.0 (16.6)	23.7 (8.3)	**0.001**
Adipsin, ng/mL	37.0 (17.7)	58.1 (18.3)	49.7 (16.4)	**0.001**

Table 1 also includes routine biochemistry tests of PCOS adolescents and healthy controls. Mean HDL-Cholesterol, triglyceride, E2, FSH, CRP and insulin levels were found to be significantly different between groups ($p<0.05$). Overweight adolescents with PCOS have higher triglyceride, FSH, CRP and insulin levels and lower HDL-Cholesterol and E2 levels than those in normal weight adolescents with PCOS and healthy controls ($p<0.05$).

Adipsin levels did not differ between total PCOS patients and healthy controls [47.0 (20.8) ng/mL vs. 49.7 (16.4) ng/mL, respectively] ($p>0.05$). When the PCOS group was divided into normal- and over-weight, adipsin levels showed statistically significant differences between the groups ($p<0.001$). Non-obese PCOS adolescents have statistically significantly higher adipsin levels than both obese PCOS adolescents and non-PCOS adolescents ($p<0.001$ and $p<0.05$, respectively) (Figure 1). At the same time, non-PCOS adolescents also have higher adipsin levels than obese PCOS adolescents ($p<0.05$)



[a] $p<0.05$ compared with non-PCOS,
[b] $p<0.001$ compared with obese-PCOS

Figure 1. Adipsin levels in PCOS and non-PCOS adolescents

When the relationships between adipsin levels and other parameters were examined in the total PCOS group, negative correlations were observed between adipsin and BMI, triglyceride, CRP and insulin (Table 2). In healthy controls, a positive correlation was observed between adipsin and LDL-cholesterol (Table 2).

Table 2. The relationship between adipsin and biochemical parameters in PCOS and non-PCOS adolescents

	Adipsin R (P)*	
	Non-PCOS	***PCOS***
BMI	-0.018 (NS)	**-0.457 (0.001)**
CHOLESTEROL	0.261 (NS)	0.151 (NS)
TRIGLYCERIDE	0.066 (NS)	**-0.260 (0.026)**
HDL	0.211 (NS)	0.103 (NS)
LDL	**0.468 (0.002)**	0.221 (NS)
E2	0.150 (NS)	0.131 (NS)
FSH	0.061 (NS)	-0.179 (NS)
LH	-0.045 (NS)	0.196 (NS)
CRP	-0.209 (NS)	**-0.378 (0.001)**
INSULIN	0.000 (NS)	**-0.302 (0.010)**

*R (P): Correlation coefficient (Significance)

4. Discussion

PCOS is reported to affect at least 1 in every 200 adolescent girls. Although the causes of PCOS development in adolescence are not fully known, some genetic and environmental factors that may create a predisposition have been identified (Saleh et al, 2024). It is thought that PCOS in childhood may show polygenic inheritance due to the influence of environmental factors. In addition, the increase in

inflammatory markers in PCOS suggests that inflammation may also be a factor, but it is not known whether it is directly involved in pathogenesis (Duleba & Dokras, 2012) A significant relationship has also been reported between obesity and the development of PCOS in children (Saleh et al., 2024) Both obese and normal weight children were included in our study.

Diagnosing PCOS in adolescence is difficult and controversial compared to adult women and based on two clinical entities: hyperandrogenism (clinical or biochemical) and menstrual irregularity. Adolescents with only one of these features can be considered "at risk" for PCOS (Burgert 2024). In recent decades, striking increases in the prevalence of overweight/obesity in girls have been accompanied by rapid maturation and marked increases in the prevalence of adolescent PCOS (Ibáñez & de Zegher, 2023). Adolescents with PCOS are observed to exhibit hyperandrogenism and insulin resistance (Siddiqui, 2022). The main diagnostic criteria for adolescent PCOS are hirsutism, acne, seborrhea, androgen excess in girls, and oligo-amenorrhea (>2 years after menarche) (Ibáñez & de Zegher, 2023; Zegher et al., 2018).

Adipsin, also known as complement factor D, is a protease with a cytokine structure and provides the relationship between adipose tissue metabolism and complement pathways. The fact that adipsin levels are associated with age, body weight, BMI, fasting plasma glucose, and leptin emphasizes the importance of adipsin in the pathophysiology of obesity, insulin resistance, and diabetes (Chedraui et al.,2014; Milek et al., 2022). Adipsin, first identified as complement factor D, also activates the alternative complement pathway and is therefore an important component of the immune system (Cook, 1985; White et al., 1992). The complement system is a part of the innate immune system and has been shown to be linked to inflammation, obesity, insulin resistance and cardiovascular disease (Hertle et al., 2012). Because of some evidence that there is a connection between the complement system and PCOS, it has been thought that adipsin may play a role in PCOS. In our study, adipsin levels were significantly higher in adolescents with PCOS than in healthy controls. However, although adipsin is a protein secreted from adipocytes, its levels were lower in obese adolescents with PCOS than in those with normal weight. This result was also confirmed by the correlation test, and a significant negative correlations were observed between BMI and adipsin and between triglyceride and adipsin in the PCOS group. In previous studies, it has also been shown in preclinical studies that adipsin levels are reduced in different animal models of obesity, (Cook et al., 1987), but human studies have found positive correlations between adipsin serum concentrations and BMI (Milek, 2022). In a recent study, similar to our results, adipsin levels found to be decreased in obese females with PCOS than those in lean females with PCOS (Tanilir Çağiran & Kali, 2024; Vejrazkova et al., 2017). In two different studies, adipsin levels were found to be higher in overweight women with PCOS than in lean women (Butler et al., 2022; Gürsoy Calan et al., 2016). However, Butler et al. found a positive correlation between BMI and complement factor D.

5. Conclusion

Confusing results have been obtained regarding adipsin levels in different diseases and conditions. Although significantly higher adipsin levels were observed in normal weight PCOS in our study, it was not found to be associated with other parameters of this disease. Since evaluations regarding adipsin levels are generally made based on adult levels, it can be considered that adipsin levels may be affected by different mechanisms in adolescents where hormonal balance is restructured. On the other hand, adipsin can be considered as an independent risk factor in normal weight PCOS adolescents and may help in the diagnosis of PCOS in normal weight children with other symptoms.

Ethics Committee Approval

The study protocol was approved by the Ethical Committe of Gazi University (dated 12.09.2022, ref.no:685)

Conflict of Interest

No conflict of interest was declared by the authors.

Authorship Contributions

Concept: ÇE, SYA, Design: ÇE, SYA, ADB, Data Collection or Processing: ÇE, ADB, YY, Analysis or Interpretation: SYA, ÇE, ADB, YY, Literature Search: ÇE, SYA, YY Writing: SYA, ÇE, ADB, YY

Acknowledgements

This study was supported by Gazi University Research Fund (Project No: TDK-2023-8311).

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