Türk Üreme Tıbbı ve Cerrahisi Dergisi
Turkish Journal of Reproductive Medicine and Surgery

ORIGINAL RESEARCH ORİJİNAL ARAŞTIRMA

DOI: 10.24074/tjrms.2023-100135

Serum Adipsin Levels of Lean and Overweight Women with Polycystic Ovary Syndrome

Zayıf ve Aşırı Kilolu Polikistik Over Sendromlu Kadınlarda Serum Adipsin Düzeylerinin Değerlendirilmesi

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ABSTRACT

Objective: To compare serum adipsin concentrations in underweight and overweight polycystic ovary syndrome. **Materials and Methods:** A total of 56 patients, 28 of whom were diagnosed with PCOS and 28 were healthy controls were included. PCOS patients were divided into two groups according to BMI values. While 14 patients with a BMI of 18.5-24.9 kg/m^2 constituted the normal weight PCOS group, 14 patients with a BMI of 25-29.9 kg/m^2 were considered overweight PCOS. No hyperandrogenemia, LH, FSH imbalance and PCO morphology were found in the control group. Serum adipsin concentration of both groups was measured by ELISA method. **Results:** Serum adipsin levels were significantly decreased in the obese PCOS group compared to lean PCOS and controls. The serum adipsin levels of the non-PCOS group showed a significant increase compared to both the lean PCOS and the obese PCOS groups. The lean PCOS group exhibited high adipsin levels compared to the obese group. There was a negative significant relationship between BMI and adipsin in both PCOS groups. The increase in BMI led to a decrease in adipsin level. A negative significant correlation was recorded between serum adipsin levels, HOMA-IR, LH and testosterone in PCOS group. **Conclusions:** Obesity impairs both synthesis and release of adipsin from adipose tissue of PCOS patients.

Keywords: PCOS, Adiposity; Adipsin; HOMA-IR; BMI

ÖZET

Amaç: Obez ve düşük kilolu polikistik over sendromu hastalarında serum adipsin konsantrasyonlarını karşılaştırmak. **Gereç ve Yöntemler:** 28'i PKOS ve 28 sağlıklı kontrol olmak üzere toplam 56 hasta çalışmaya dahil edildi. PKOS grubu BMI değerlerine göre iki gruba ayrıldı. BMI 18,5-24,9 kg/m^2 olan 14 hasta normal kilolu PKOS grubunu oluştururken, BMI 25-29,9 kg/m^2 olan 14 hasta fazla kilolu kabul edildi. Her iki grubun plazma adipsin konsantrasyonu ELISA yöntemiyle ölçüldü. **Bulgular:** Serum adipsin düzeyleri obez PKOS grubunda zayıf PKOS ve kontrollere göre anlamlı derecede düşük idi. Kontrol grubun serum adipsin düzeyleri hem zayıf PKOS hem de obez PKOS gruplarına kıyasla anlamlı artış gösterdi. Zayıf PKOS grubu, obez gruba kıyasla daha yüksek adipsin seviyeleri sergiledi. Her iki PKOS grubunda BMI ile adipsin arasında negatif anlamlı ilişki vardı. BMI'daki artış adipsin düzeyinde azalmaya yol açtı. PKOS gruplarının serum adipsin düzeyleri ile HOMA-IR, LH ve testosteron arasında negatif ve anlamlı bir korelasyon saptandı. **Sonuç:** Obezite, PKOS hastalarında adipoz dokunun adipsinin sentez ve salınımını bozar.

Anahtar Kelimeler: PKOS; Adipozite; Adipsin; HOMA-IR; BMI

TO CITE THIS ARTICLE:
Kalı Z, Tanılır Çağıran F. Serum Adipsin Levels of Lean and Overweight Women with Polycystic Ovary Syndrome. Turkish Journal of Reproductive Medicine and Surgery. 2024;8(2):42-7.

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Peer review under responsibility of Turkish Journal of Reproductive Medicine and Surgery.

Received: 06 Nov 2023 ***Received in revised form:*** 05 Jun 2024 ***Accepted:*** 13 Jun 2024 ***Available online:*** 04 Jul 2024

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in the reproductive age and progressing with subfertility. It occurs due to a defect in the release of hormones in the hypolamus-pituitary-ovarian axis. Although the main clinical finding of PCOS is ovulatory dysfunction, it allows the development of clinical and laboratory problems due to increased androgen production. Increased androgen levels cause disruptions in insulin secretion and postreceptor effects of insulin.[1-3] As the endocrine and paracrine effects of adipose tissue will be disrupted due to insulin resistance, the balance between lipogenesis and lipolysis is disturbed. Adipose tissue functions as an energy store under normal conditions and contributes to metabolic balance by regulating the release of molecules called adipokines. PCOS is characterized by defects in endocrine and paracrine functions of adipose tissue. In the presence of PCOS, the release of some adipokines increases, while others decrease and some remain unchanged. Adipokine synthesis and secretion defect leads to worsening of the metabolic picture, mainly obesity, subfertility and deterioration in insulin hemostasis.[1-3]

Hundreds of different adipokines are synthesized and secreted from adipose tissue. These molecules are in protein structure and have critical importance in the regulation of cell metabolism. Adipsin is one of the main adipokines derived from adipose tissue. Adipsin is also known as complement factor D. Thanks to its complement feature, adipsin is involved in the protection of beta cells of the pancreas. The main task of adipsin is to increase the insulin response to glucose.[4,5] There are clinical and experimental studies examining serum adipsin level changes in metabolic diseases. It has been reported that women with type 2 diabetes had low serum adipsin levels.[6,7] There are limited studies investigating serum adipsin levels in PCOS patients, and their results are heterogeneous.[1,2] In previous studies, PCOS patients were pooled in the same pool without discriminating between underweight or obese. It is not surprising that the results are heterogeneous, since patients are not grouped according to body mass index values. Our study was designed to determine serum adipsin levels by dividing patients diagnosed with PCOS into groups according to their BMI values. Possible correlations between serum adipsin levels and metabolic, hormonal and demographic parameters were also reviewed.

MATERIALS AND METHODS

The study sample included a total of 56 patients, 28 of whom were diagnosed with PCOS according to the Rotterdam criteria and 28 were healthy controls. Patients with at least two of the following criteria were considered PCOS; [1] chronic ovulatory dysfunction, [2] clinical or laboratory findings of hyperandrogenemia, [3] detection of 12 or more follicles between 2 and 9 mm in ultrasound examination. PCOS group was divided into two groups according to BMI values. While 14 patients with a BMI of 18.5-24.9 kg/m^2 constituted the normal weight PCOS group, 14 patients with a BMI of 25-29.9 kg/m^2 were considered overweight PCOS. In the evaluation of the patients in the control group, no hyperandrogenemia, LH, FSH imbalance and PCO morphology were found. Participants of both groups were recruited from the Gözde Akademi Hospital Gynecology outpatient clinic. The study was initiated after SBU Gazi Yaşargil Training and Research Hospital ethics committee approval and patient consent were obtained (Ethics approval no: 276/2022). Strict compliance with the Declaration of Helsinki was demonstrated throughout the study.

Fasting blood samples were taken for basal hormone, insulin and adipsin evaluation. Serum adipsin concentration of both groups was measured by ELISA method. Venous blood samples were collected the morning following an overnight fast. Collected blood samples of both groups of participants were centrifuged and aliquots were stored until analysis. Circulating luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, glucose and insulin levels were measured. Homeostatic Model Assesment of Insulin Resistance (HOMA-IR) değerleri [Fasting glucose (mg/dL)×Fasting insulin (uIU/mL)/405] formülü ile hesaplandı.[8] Those with systemic disease, other endocrinopathy, and

those using hormonal drugs for 3 months or more were excluded from the study. The aim of the study was to analyses serum adipsin concentrations of lean and overweight women with PCOS. Secondary aim was to reveal the correlation between serum adipsin, demographic, hormonal, and metabolic parameters.

ADIPSIN MEASUREMENT WITH ELISA

Serum concentration of adipsin in PCOS and control groups were measured in accordance with the procedures specified in the Human adipsin ELISA Kit (Bioassay Technology Laboratory, Shanghai, China). Intra- and inter-assay CV values of the kit were <8% and <10%, respectively. Test results were expressed in ng/mL. The standard curve range of the kit was 0.1 ng/mL-40 ng/mL, and the minimum measurable level was 0.047 ng/mL.

STATISTICAL ANALYSIS

All data were analyzed with SPSS 25.0 for Windows software. The pattern of data distributions was analyzed with the Shapiro-Wilk test. Normally distributed numerical data were analyzed with the Student-t test, and abnormally distributed numerical data were analyzed with the Mann-Whitney U test. If the normally distributed parameter consisted of more than two groups, One-Way ANOVA test was applied. Parameters that did not show normal distribution were compared with the Kruskal-Wallis test. Bonferroni test was used for post-hoc pairwise comparisons. Pearson or Spearman correlation analysis was used to evaluate the relationships between parameters. Data is given as mean±SD or median (1st quartile-3rd quartile). $p<0.05$ was considered statistically significant.

RESULTS

The mean age of women in the PCOS (24.39±3.35) and non-PCOS control (25.32±3.28) groups were similar (p=0.234). The BMI of the PCOS group [25.0 (23.81-28.25)] was higher than the BMI of the control group [24.0 (23.0-24.29) ($p<0.001$)]. The BMI values of the obese PCOS group were higher than both the lean PCOS and the control group (for each $p<0.001$). The LH values of the control group were lower than the overweight PCOS group and the lean PCOS group (for each $p<0.001$). FSH values were similar in each group of participant. Serum androgen levels of the lean and obese PCOS groups were similar ($p>0.05$). Patients in each PCOS group had higher androgen levels compared to the control group (for each $p<0.001$). The HOMA-IR value of the obese PCOS group was significantly higher than control group (p=0.006). There was no difference in HOMA-IR between Lean PCOS and the control group. The blood glucose values of the obese PCOS group were higher than the control and lean PCOS groups (Table 1).

Serum adipsin levels were significantly lower in the obese PCOS group than in the lean PCOS and control group. Serum adipsin levels of the control group were significantly higher than the lean and

TABLE 1: Comparison of demographic, metabolic and hormonal findings of lean and obese women with PCOS and control groups.

	Lean PCOS (n=14)	Overweight PCOS (n=14)	Control (n=28)
Age (years)	24.07±3.36	24.71±3.43	25.32±3.28
BMI (Kg/m^2)	23.93 (22.21- 24.58)	28.09 (26.62- 29.06) $^{a<0.001, b<0.001}$	24.0 (23.0- 24.29)
Adipsin (ng/mL)	15.19±5.88 a<0.001	7.41±5.21 a<0.001, $^{b<0.001}$	21.6±4.14
LH (mIU/mL)	8.26 (7.70-9.56) a<0.001	11.17 (10.76-12.44) $^{a<0.001}$	5.32 (4.87-5.70)
FSH (mIU/mL)	5.27 (4.57-5.71)	5.21 (4.70-5.48)	5.0 (4.53-5.70)
Testosterone (ng/dL)	45.87±8.23 a<0.001	46.52±4.91 $^{a<0.001}$	34.36±9.65
Glucose (mg/dL)	86.28±8.79	109.1±13.04 $^{a<0.001, b<0.001}$	84.36±13.6
HOMA-IR	2.22 (1.79-3.17)	4.19 (1.80-5.38) $^{a=0.006}$	1.75 (1.56-2.30)

Data are presented Mean±SD or median (1st quartile-3rd quartile) according to normality of distribution. [a]: comparison with control group, [b]: comparison with normal weight PCOS

TABLE 2: Correlation analysis of serum adipsin levels and hormonal parameters of lean and obese women with PCOS.

	Lean PCOS Adipsin		Overweight PCOS	
	r	*P*	*r*	*p*
Age	0.383	0.176	0.174	0.552
BMI	-0.670	**0.009**	-0.780	**<0.001**
LH	-0.543	**0.045**	-0.596	**0.025**
FSH	0.341	0.233	-0.376	0.185
Testosterone	-0.536	**0.048**	-0.736	**0.003**
Glucose	-0.060	0.839	-0.495	0.072
HOMA-IR	-0.714	**0.004**	-0.688	**0.007**

r: Correlation coefficient

obese PCOS groups. Serum adipsin levels were significantly higher in the thin PCOS group than in the obese group. A negative and significant correlation was found between BMI and adipsin values in the PCOS group. The increase in BMI led to a decrease in adipsin level. A negative and significant correlation was found between serum adipsin levels and HOMA-IR, LH and testosterone levels in both PCOS groups. There was no correlation between serum adipsin levels and demographic, metabolic and hormonal parameters in the control group (Table 2).

DISCUSSION

Polycystic ovary syndrome is a complex endocrine disease that brings with it different problems according to the age group in which it occurs. Clinical findings related to ovulatory dysfunction, obesity and hyper androgenemia are prominent in the adolescent group. In women of reproductive age, the main complaint is subfertility. In advancing age groups, however, metabolic disorders, diabetes, and the risk of transformation into premalignant and malignant diseases of the endometrium.[1-3] The main reason why we do not have a magic wand about PCOS is that we do not know the causes of the disease. In fact, PCOS, which has a multifactorial etiology, was initially believed to develop due to LH/FSH secretion imbalance. However, it would not be correct to attribute the abundance of follicles and morphological changes in the ovaries to the LF/FSH imbalance only. Pathological changes in the ovary may cause LH pulsation disorder, as well as primary release defect of LH may disrupt ovarian morphology.[2,3] Since the connection between androgen elevation and insulin resistance disrupts the dynamics of adipose tissue, the balance of lipogenesis and lipolysis is disturbed, and most of the PCOS patients tend to obesity. However, lean PCOS cases weaken our opinion.

One of the main target organs of PCOS patients is adipose tissue. In the presence of PCOS, there are deviations from physiological adipokine synthesis and release in both peripheral adipose tissue and visceral adipose tissue.[9,10] Adipsin is one of the most important adipokines secreted from adipose tissue.[4,5] Similar to other adipokines, adipsin also plays a role in glucose-insulin hemostasis. Adipsin responds to the increase in glucose by increasing insulin secretion from the pancreas. Adipsin, a member of the serine protease family, has a privileged place as it stimulates insulin secretion and protects pancreatic beta cell functions through complement activity.[11] We found that serum adipsin values were significantly higher in the lean PCOS group than in the obese group in the patients we divided into two groups according to their BMI values. Obesity led to a significant decrease in serum adipsin values. The negative and significant correlation between BMI values and adipsin values is an important proof that adiposity negatively affects adipsin release. The negative correlation between BMI and adipsin in the

lean PCOS group suggests that adipsin synthesis is impaired in PCOS patients, independent of BMI. However, as BMI increases, the defect in adipsin secretion becomes more obvious. The fact that both PCOS phenotypes are similar in terms of the negative correlation between LH, testosterone, HOMA-IR values and adipsin suggests that adiposity negatively affects metabolic parameters regardless of BMI values. Since impaired adipsin production will also impair beta cell functions, it suggests that the risk of developing type 2 diabetes is high in long-term PCOS patients.

The results of studies on PCOS and adipokine levels are heterogeneous. Adipokines differ according to patient phenotypes. Hyperandrogenemia and high BMI levels stand out as the parameters that most affect adipokine production.[2] The negative correlation between adipsin levels and high androgen levels in our study is consistent with the literature data. The negative correlation between BMI values and adipsin suggests that BMI blocks adipsin synthesis. However, high BMI values normally result in high adipocytokine synthesis. The reason for the decreased adipsin levels in our study may be due to the low number of participants in the PCOS cohort. Despite the limited number of cases, our results are important because it is the first study to analyze serum adipsin levels in lean obese PCOS. It is important to classify PCOS according to phenotypes and metabolic syndrome and to investigate adipsin levels in order to give clearer results.

CONCLUSION

It is difficult to make a clear interpretation of how adipose tissue, which is responsible for the synthesis and release of approximately 600 adipokines, changes in PCOS.[9,10] Our study is important in terms of presenting the first findings investigating the change in serum adipsin values according to BMI values of PCOS patients. In the presence of obesity, PCOS patients synthesize low adipsin, whereas in lean PCOS patients, adipsin synthesis is close to controls. In the light of these data, controlled reduction of BMI in PCOS patients will both increase adipsin levels and prevent the development of diabetes by protecting pancreatic beta cells. Thanks to longitudinal studies with high participants, the effects of adipsin and other adipokines on adiposity and pancreatic functions can be revealed more clearly.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Fatma Tanılır Çağıran;* ***Design:*** *Zercan Kalı;* ***Control/Supervision:*** *Fatma Tanılır Çağıran;* ***Data Collection and/or Processing:*** *Fatma Tanılır Çağıran, Zercan Kalı;* ***Analysis and/or Interpretation:*** *Fatma Tanılır Çağıran, Zercan Kalı;* ***Literature Review:*** *Zercan Kalı;* ***Writing the Article:*** *Fatma Tanılır Çağıran, Zercan Kalı;* ***Critical Review:*** *Zercan Kalı;* ***References and Fundings:*** *Fatma Tanılır Çağıran;* ***Materials:*** *Fatma Tanılır Çağıran.*

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