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# ADIPONECTIN AS A SERUM MARKER OF ADIPOSE TISSUE DYSFUNCTION IN WOMEN WITH POLYCYSTIC OVARY SYNDROME: CORRELATION WITH INDICATORS OF METABOLIC DISTURBANCES

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**Abstract**

Adipose tissue is a major store of energy for the human body. Polycystic ovary syndrome (PCOS) patients are more prone to abnormal production of some regulatory proteins secreted from the adipose tissue. This study aims to investigate serum levels of adiponectin and their correlation with metabolic and endocrine indices in PCOS.

**Patients and methods.** This study was conducted on 61 women with PCOS and 17 healthy women whose age and body mass index (BMI) were matched. Adiponectin serum levels were assessed and correlated with parameters of metabolic and hormonal disturbances.

**Results.** In PCOS women, serum levels of insulin, HOMA-IR, testosterone, LH, and LH/FSH were significantly higher, while SHBG was lower than in healthy women. Lower adiponectin was observed in both PCOS groups compared to the control group. Serum levels of adiponectin correlated inversely with BMI (r=- 0.56; p<0.001),WC(r = -0.452;p<0.001), insulin levels (r= - 0.409; p<0.001), HOMA-IR (r= -0.368; p<0.001), and free androgen index (FAI) (r= - 0.53; p<0.001). A positive correlation was found between adiponectin and LH (r= 0.35; p<0.001), LH/FSH ratio (r= 0.33; p<0.001) and SHGB (r= 0.51; p<0.001). Serum adiponectin levels are decreased in women with PCOS compared to the control group. The decrease in adiponectin concentration indicates its potential role in metabolic disorders in the pathogenesis of PCOS, as well as in the development and progression of insulin resistance in PCOS patients.

**Key words:** Polycystic ovary syndrome, obesity, adipocytokines, adiponectin, insulin resistance.

## INTRODUCTION

Adipose tissue plays essential metabolic roles and does not have just a passive role of massive energy storage. There is rising data leading to the notion that accumulated adipose tissue is an endocrine organ that can produce a great number of bioactive peptides and proteins – cytokines (1, 2). Some of these adipokines have a central role in the development of obesity-related and metabolic complications or are involved in different functions in the organism including reproduction function. Several lines of evidence suggest that obesity and female reproduction are interrelated.

Polycystic ovarian syndrome (PCOS) is one of the most frequent reproductive dysfunctions globally present with 7-10%, and mostly related to obesity (3). It is estimated that the prevalence of obesity in women with PCOS, depending on population or the studied ethnic group, varies from 30-75% (4). The pathogenesis of this endocrine condition is not fully clarified raising great interest mainly because of the metabolic consequences that arise from its existence. The presence of obesity in PCOS women magnifies insulin resistance and is one of the main risk factors which seem to have an important role in the progress and appearance of the clinical, biochemical, and metabolic features of PCOS (5). Insulin resistance also causes predisposition to type visceral obesity, emulating the androgen-like phenotype of PCOS (6). Growing evidence shows that the irregular secretion of adipokines plays an important role in the patho physiology of PCOS. Adiponectin is a cytokine synthesized and secreted solely in the adipose tissue. Its concentration in the blood ranges from five to 30 mg/mL and about 0.01% of the total plasma proteins belong to it. The adiponectin gene is positioned on the chromosome 3q27, at a locus for diabetes susceptibility (7, 8). Adiponectin is defined as a "beneficial adipokine" in reproduction (9). In human hypothalamus and pituitary, both ADIPOR1 and ADIPOR2 receptors are expressed and it has been shown that adiponectin inhibits luteinizing hormone

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(LH) and gonadotropin-releasing hormone (GnRH) secretion (10), indicating its possible role in modulating the central reproductive endocrine axis (11). Studies investigating the changes of the serum adiponectin report opposing results. To the best of our knowledge, there is no study which evaluates adiponectin levels in a Macedonian cohort of women of reproductive age with PCOS. The aim of this study was to assess the levels of adiponectin in patients with PCOS and normal ovulatory women. Furthermore, in this report, we describe the correlations between adiponectin, anthropometric measures, metabolic factors and insulin resistance.

## MATERIALS AND METHODS

This study was performed at the Clinical Chemistry Department, University Clinic of Gynecology and Obstetrics, Republic of Macedonia. All investigations are carried out according to the Declaration of Helsinki, following informed consent. The study and all actions involving human subjects/ patients were approved by the Ethical Committee for research on people and animals at the Faculty of Medicine, Skopje, University Ss "Cyril and Methodius" Skopje R. Macedonia.

### *Study population*

This study was designed as a cross-sectional and involves 78 premenopausal women. Of all patients, 61 females aged 20-38 years had PCOS diagnosis according to the Rotterdam ESHRE/ ASRM-Sponsored PCOS Consensus Workshop Group (12). The control group consisted of 17 healthy normo ovulatory, nonpregnant women, without clinical or biochemical signs of hyperandrogenism and with no prior known endocrine disease. Patients with thyroid disorders, hyperprolactinemia, renal or hepatic dysfunction, diabetes type 1 or 2, congenital adrenal hyperplasia, and Cushing's syndrome or neoplastic diseases, were excluded from the study. Additionally, patients who received medication as hormonal supplementation three months prior to the study, insulin sensitizers or corticosteroids were also excluded. All subjects received information about the protocol and they had signed a written consent. A statistical power analysis was performed using G*Power 3.1 software calculator (13). The effect size (ES) in this study was 1.37, for $\alpha$=0.05 and power of 0.90, the projected size needed with this effect size is approximately of N=26 total sample size, for within group comparison. After collecting patient samples for the study, we have carried out post-hoc analysis and achieved a power of 0.99.

### *Measurement of Anthropometric Characteristics*

A single investigator in all subjects determined clinical and anthropometrical variables. Body mass index (BMI) was calculated according to the standard formula as follows: weight in kilograms divided by the height in meters squared (kg/m$^2$). Waist circumference (WC) was measured midway between the superior border of the iliac crest and the lowermost margin of the ribs, using a waistline measurer employed with subjects standing without clothing covering the waist area. Hip circumference (HC) was obtained at the point with the maximum circumference over the buttocks. The waist-to-hip ratio (WHR) is defined as the waist circumference/hip circumference. Based on the WHO classification, the whole cohort of PCOS patients was divided according to their BMI into two groups: group A: normal weight PCOS (BMI $\leq$24.9 kg/m$^2$, n =24) and group B: obese PCOS (BMI > 25 kg/m$^2$, n = 37) and group C: (control group, n=17). Transvaginal ultrasound scan of the ovaries was performed at the University Clinic of Gynecology and Obstetrics, using a 6.5 MHz transducer in order to determine the total number of early antral follicles. The PCO morphology has been defined by the presence of 12 or more follicles 2–9 mm in diameter and/or an increased ovarian volume >10 mL (without a cyst or dominant follicle) in either ovary (14).

### *Biochemical measurements*

All blood samples were taken from subjects after 12-14 hours overnight fasting in the follicular phase between the 3$^{rd}$ and 7$^{th}$ day of a spontaneous cycle or at any given day in women with absent menstrual cycle in the previous two or more months. Subsequently, follicle – stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), Estradiol (E2), total testosterone (TES), dehydroepiandrosterone sulfate (DHEAS), androstenedione (AND), Sex Hormone Binding Globulin (SHBG), insulin and glucose (GLU) were measured. Blood samples were withdrawn between 08:00 and 10:00 h AM from an antecubital vein after 5 min rest in the supine position. Samples were kept for at least 30 minutes, and then centrifuged. The resulting serum and plasma were aliquoted, frozen and maintained at -40˚C until adiponectin measurement.

***Glucose homeostasis, Insulin resistance***

Insulin resistance may be obtained using various methods (14, 15). We have chosen to use the model of static fasting glucose and insulin measurements, and the same correlate highly with dynamic measurements by glucose loading (16). The presence of IR was evaluated by using basal fasting insulin concentrations, fasting glucose concentrations and homeostasis model assessment (HOMA-IR). Homeostasis model assessment for insulin resistance evaluation (HOMA-IR) was calculated using the equation: fasting insulin μU/ml × glucose (mmol/L) /22.5 (17).

***Laboratory procedures***

Fasting levels of plasma glucose were measured immediately after venepunction using the enzymatic glucose oxidase method (Cobas Integra 400 plus, Roche Diagnostic). All hormonal assays were evaluated using the Immulite 2000 HP, Diagnostics Products Corp. Serum FSH, LH, PRL and SHBG are determined by solid-phase, two–site chemiluminescent immunometric assay, with lower limits of sensitivity 0.1 IU/L, 0.05 IU/L, 10.6 mIU/L and 0.2 nmol/L respectively. The respective intra - and inter-assay coefficients of variation were 2.0% and 4.5% for FSH, 2.6% and 5.4% for LH and 1.5 % and 2.5% for PRL and 4.6% and 2.9% for SHGB. Serum estradiol and INS were measured by solid-phase, enzyme labeled chemiluminescent immunometric assay with lower limits of sensitivity of 20.0 pmol/L, and 2.0 mIU/L, respectively; the respective intra - and inter-assay coefficients of variation were 1.4% and 4.9% for E2, and 3.2% and 3.0% for INS. Serum total testosterone, DHEA-S and AND were measured by solid-phase, competitive chemiluminescent enzyme immunoassay, with lower detectable concentrations of 0.1 nmol/L, 0.08 μmol/L and 1.0 nmol/L, respectively and inter- and intra-assay coefficients of variation were 5.3% and 5.4% for TES, 4.7% and 8.3% for DHEA-S and 4.3% and 5.2% for AND. The free androgen index (FAI) was calculated according to the standard equation: total testosterone (nmol/L) x 100/ SHBG (nmol/L)(18).

Levels of the total adiponectin were measured by an ELISA competitive enzyme immunoassay for quantitative measurement of the human adiponectin, using commercially available kits (BV51001 Human Adiponectin). The lower detectable concentrations were 0.1μg/mL for adiponectin and inter- and intra-assay coefficients of variation 4.9% and 6.3%, respectively.

***Statistical analysis***

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 17.0 for Windows, SPSS Inc., Chicago, IL, USA). Results are expressed as the mean ± standard deviation (S.D). The characteristics of distribution were tested with the Shapiro-Wilks W test. Because of the skewed distribution of the parameters, we used log-transformed values in the subsequent statistical analysis. The clinical and laboratory characteristics in the groups were compared by analysis of variance (ANOVA test). Means between every group of every parameter were compared with post hoc ANOVA. Bivariate correlation analysis (calculation of the Pearson coefficient) was used to explore the possible correlation of adiponectin level to each parameter. A forward stepwise multiple regression model was calculated for patients with PCOS using serum adiponectin as a dependent variable, to calculate the influences of independent variables. For all analysis, a P-value less than 0.05 was considered statistically significant.

## RESULTS

In this study, 78 women enrolled and 61 patients were diagnosed as having PCOS according to Rotterdam diagnostic criteria. Oligomenorrhea or amenorrhea was noted in 58 (95.1%), biochemical hyperandrogenism was found in 54 (75%), hirsutism in 37 (60.7%), acne in 22 (36.1%) and polycystic ovaries on ultrasound among 50 (83.3%). The clinical and anthropometric characteristics of studied groups are presented in Table 1. The age of women was between 21- 31, with an average age of the patients in the control group higher (26.52 ± 5.1 years) in comparison to the PCOS group, but not statistically significant. A statistically significant difference was found in the BMI, WC, HC and WHR in obese patients with PCOS compared to the control group.

As expected in both PCOS groups FSH, LH, LH/FSH ratio, testosterone and FAI are significantly higher, compared with the control group of women. Significantly, lower concentration of SHGB is found in obese PCOS women. In addition, FAI was significantly higher in obese PCOS than in normal weight PCOS group. There was no statistical difference in testosterone levels between PCOS groups, but higher compared to control group. Serum concentrations of fasting glucose, fasting insulin, and HOMA-IR value were significantly higher in both PCOS groups compared to control. Fasting insulin values and HOMA-IR were statistically

**Table 1.** Anthropometric, hormonal and metabolic characteristics

| Variable | Group A: normal weight PCOS (BMI ≤24.9 kg/m$^2$, n=24) | Group B:obese PCOS (BMI > 25 kg/m$^2$, n=37) | Group C: control group (BMI ≤24.9 kg/m$^2$, n=17) |
|---|---|---|---|
| Age(years) | 24.17±3.3 | 24.32±4.3 | 26.52±5.1 |
| BMI(kg/m$^2$) | 21.9±1.9 | 31.63±5.1[a,c] | 20.95±2.5 |
| Waist circumference(cm) | 82.65±8.2 | 105.03±12.0[a,c] | 77.29±8.43 |
| Hip circumference(cm) | 98.3±7.1 | 116.8±11.7[a,c] | 98.3±9.6 |
| WHR | 0.84±0.05 [b] | 0.90±0.08 [a,c] | 0.78±0.03 |
| **Hormonal parameters** | | | |
| FSH(IU/L) | 5.58± 1.2 [b] | 5.66 ± 2.1[c] | 7.15±1.0 |
| LH(IU/L) | 11.82 ± 4.7 [b] | 7.84 ± 4.1[a, c] | 4.63±1.3 |
| LH / FSH | 2.16 ± 0.8 [b] | 1.5 ± 0.9 [a, c] | 0.66±23 |
| PRL(ng/mL) | 11.43 ± 4.8 | 11.42 ± 5.5 | 13.11±6.2 |
| E2(pmol/L) | 57.31±23.9 | 55.9 ± 22.1 | 45.7±12.4 |
| TSH(mIU/L) | 2.56 ± 2.4 | 2.1 ± 0.7 | 2.2±0.8 |
| DHEAS (µg/ml) | 3.52± 2.7[b] | 3.93 ± 2.0[c] | 2.1±0.78 |
| Testosterone (nmol/L) | 2.23 ± 0.8 [b] | 2.3 ± 0.9 [c] | 0.89±0.31 |
| Androstendione(ng/mL) | 5.36 ±2.1 [b] | 5.1 ±1.6 [c] | 2.25±0.75 |
| FAI% | 5.15 ± 2.8 [b] | 12.22 ±8.1[a, c] | 1.6±1.0 |
| SHBG (nmol/L) | 50.37±24.6 | 22.81±10[a, c] | 62.15±21.08 |
| **Metabolic parameters** | | | |
| Fasting glucose(mmol/L) | 5.25±0.4[b] | 5.33±0.4[c] | 4.9±0.2 |
| Fasting insulin(mIU/L) | 7.55±4.4 [b] | 17±6.8[a, c] | 5.4±3.4 |
| HOMA-IR | 1.74±1.0 [b] | 3.97±1.6[a, c] | 1.19±0.7 |
| Adiponectin (ng/mL) | 14.25±4.1[b] | 10.12±4.8[a, c] | 19.18±6.2 |

Data are presented as mean ± standard deviation (SD). Comparison is performed between PCOS N women, PCOS H woman and control group with Student's T-test. a: p < 0.01 when group A compared with group B; b: p<0.01 when group A compared with group C; c: p <0.01 when group B compared with group C (PCOS: polycystic ovary syndrome; BMI: body mass index; WHR: waist to hip ratio; FSH: follicle stimulating hormone; LH: luteinizing hormone; PRL: prolactin; E2: estradiol; TSH: tireostimulating hormone; DHEA-S: dehydroepiandrosterone sulfate; FAI: free androgen index-calculated; SHBG: Sex hormone binding globulin; HOMA-IR: Homeostasis Model Assessment–Insulin Resistance).

significantly higher in obese PCOS group compared to normal weight PCOS group. The serum adiponectin was lower in PCOS groups, with the lowest levels among obese PCOS patients.

Results of the correlation analysis tests for adiponectin with clinical, metabolic, and hormonal parameters in the group of PCOS women are presented in Table 2.

In PCOS patients, adiponectin levels correlated both negatively and significantly with the waist circumference, BMI, FAI, fasting insulin, and HOMA-IR. Adiponectin had a significant positive correlation with the SHBG, and correlated both with the LH and LH/FSH ratio. Adiponectin levels had no significant correlation with WHR, fasting glucose, FSH, PRL, E2, TES, DHEA-S.

Multiple regression analyses were performed for the PCOS patients to identify the best predictors for adiponectin levels. A waist circumference, LH, LH/FSH ratio, SHGB, fasting insulin, HOMA-IR and BMI, were included as independent explanatory variables for adiponectin as a dependent variable. The results from multiple regression analysis are presented in Table 3.

**Table 2.** Correlation between metabolic parameters and adiponectin in patients with PCOS

| | r |
|---|---|
| **Age(years)** | r = - 0.0005 |
| **BMI(kg/m$^2$)** | r = - 0.563** |
| **WC(cm)** | r = -0.452** |
| **WHR** | r = - 0.125 |
| **FSH(IU/L)** | r = 0.146 |
| **LH(IU/L)** | r = 0.35* |
| **LH/ FSH** | r = 0.337* |
| **PRL(ng/mL)** | r = 0.033 |
| **E2(pmol/L)** | r = 0.034 |
| **TES(nmol/L)** | r = - 0.106 |
| **DHEA-S(µg/mL)** | r = - 0.192 |
| **FAI %** | r = - 0.532** |
| **SHBG(nmol/L)** | r = 0.511** |
| **Fasting glucose(mmol/L)** | r = - 0.0076 |
| **Fasting insulin(mIU/L)** | r = - 0.409** |
| **HOMA-IR** | r = - 0.368** |

Pearson's correlation * p < 0.01, **p<0.001.
PCOS: polycystic ovary syndrome; BMI: body mass index; WHR: wait to hip ratio; FSH: follicle stimulating hormone; LH: luteinizing hormone; PRL: prolactin; E2: estradiol DHEA-S: dehydroepiandrosterone sulfate; FAI: free androgen index-calculated; SHBG: Sex hormone binding globulin; HOMA-IR: Homeostasis Model Assessment–Insulin Resistance.

**Table 3.** Influence of metabolic characteristics on adiponectin in women with PCOS

| | Unstandardized coefficients | | Standardized coefficients | t | Sig. |
|---|---|---|---|---|---|
| | B | Std. Error | Beta | | |
| **(Constant)** | 20.257 | 3.665 | | 5.527 | 0.000 |
| **BMI** | -.244 | .120 | -.266 | -2.045 | .045 |
| **SHBG** | .088 | .023 | .351 | 3.802 | **.001** |
| **HOMA-IR** | -.793 | .215 | -.333 | -3.683 | **.001** |

*dependent variable adiponectin, adjusted for BMI.
Multiple regression analysis model with adiponectin as a dependent variable, adjusted for BMI, according to characteristics of women with PCOS.
BMI: body mass index; SHBG: Sex hormone binding globulin; HOMA –IR: Homeostasis Model Assessment–Insulin Resistance.

After adjustment for BMI, we observed that SHBG and HOMA -IR were the strongest independent predictors for adiponectin levels ($\beta = 0.351$ and $\beta = 0.333$, $P < 0.001$ respectively).

## DISCUSSION

Polycystic ovary syndrome is one of the most complex disorders known in modern medicine and it is present in a significant portion of the female population. This syndrome is not only the most common underlying cause of anovulation in women in the reproductive period, but it is also associated with metabolic disturbances mostly as a result of dysfunctions of the insulin action. Higher prevalence of visceral adiposity 54% and obesity 49% is seen in the women with PCOS when compared with healthy women (19). Obesity in POCS women may be due to increased insulin resistance (20). Adiponectin, an adipokine secreted from adipose tissue, may be an early marker of metabolic dysregulation. Physiologically, adiponectin inhibits the differentiation of adipocytes in a paracrine manner. When the endothelial barrier is injured, adiponectin accumulates in the subendothelial space of the vascular walls. It has antiatherogenic and anti-inflammatory properties and its production decreases with increased volume of adipocytes. As designated above, in recent years, there is rising data pointing to the fact that adipose tissue imbalance may contribute to the metabolic disturbances in PCOS. However, published data of the studies evaluating levels of circulating adipokines in PCOS are inconsistent. This opposing data may appear because of heterogeneity of studied groups, different ethnical background in terms of body fat distribution and nutritional habits, resulting in changes in circulating adipokines and their different impact in promoting the insulin resistance and/or dysfunction of pituitary-gonadal axis.

In our study, for the first time, we have evaluated serum levels of the adiponectin in the women with PCOS and control group in a Macedonian cohort of women of reproductive age. Our results are in line with those of previous studies, supporting the evidence that adiponectin levels are lower in the PCOS women compared to healthy controls (21, 22). Furthermore, adiponectin levels are significantly lower in both groups- normal weight as well as in obese PCOS women, confirming the fact that the adiponectin levels are lower in PCOS independent of obesity, which was taken as a group-dividing factor. Our data are in line with previously published studies, demonstrating support for the presence of lower adiponectin in women with PCOS, irrespective of obesity (23, 24).

Women with PCOS are more prone to truncal obesity and development of metabolic syndrome with abnormal glucose metabolism and IR. Our data demonstrates that the adiponectin levels are negatively associated with the degree of obesity in women with PCOS. We found a strong negative correlation with BMI and WC implicating that increasing BMI and/or abdominal obesity also contributes towards lower adiponectin levels. Adiponectin is the only adipokine that is suppressed by increasing body fat. Several studies showed the inverse correlation between adiponectin and BMI independent of age, and lower adiponectin levels in obese PCOS women compared to normal-weight PCOS women and control group (21, 22).

Our results also led to the conclusions that adiponectin levels are lower in women with PCOS even in a group with PCOS with normal weight. We did not find a correlation between WHC and adiponectin levels. We assume that it is possible for it to be due to the different distribution of adipose tissue in our type of women (Mediterranean) compared with other European countries and America where obesity and generally visceral obesity is more pronounced. Our studied group of women with PCOS were relatively at a young age, and this may be an additional factor to why we have not achieved a correlation between adiponectin levels and WHR.

In the present study, we have found a positive correlation between adiponectin and LH and LH/FSH ratio. Adipose tissue cytokine - adiponectin may be tangled in disturbed gonadotropin release by the pituitary gland as observed in PCOS and this may be

related to the positive correlation that we have observed among adiponectin and LH, and the LH/FSH ratio. Olszanecka-Glinianowicz *et al.*, also found a relation between adiponectin and FSH, LH and LH/FSH ratio, proposing a hypothesis that adipokines may participate in dysregulation of the pituitary–ovarian axis in PCOS (23). Adiponectin receptors (ADIPOR1, ADIPOR2) are identified in human pituitary in FSH, LH, GH, and TSH-producing cells. In the pituitary gland, it appears that adiponectin has a putative role in the autocrine/paracrine control and regulation of the release of somatotrophs and gonadotrophs (11). In this study, we did not find a correlation between adiponectin and FSH levels. Taking into account the interrelation between the hypothalamic-ovarian axis and adipose tissue, adiponectin may have a role in hormonal dysregulation in PCOS.

Ardawi and Rouzi explain that lower adiponectin levels in PCOS are not determined by BMI, and they do not support a direct link between adiponectin and PCOS associated insulin resistance (24). Disturbances in insulin secretion leading to the development of insulin resistance are most evident when accompanied with obesity and are often present in PCOS women. Even when obese women with PCOS have similar trunk/peripheral fat ratios with the healthy women, they are less sensitive to insulin action (25). This study showed that fasting insulin and HOMA –IR, as indicators for insulin resistance, were significantly higher in PCOS women, with or without obesity than in the control group of healthy women. Correlation analysis in our study presented an inverse correlation between adiponectin and the HOMA - IR index and fasting insulin levels. Our findings point out that low adiponectin levels might be involved in the development of insulin resistance in PCOS patients. Orio *et al.* previously reported this in his study (22); however, it was not associated with BMI. Obesity linked adiponectin downregulation might be the mechanism through which obesity can influence the development of insulin resistance. This association confirmed by the results of multivariate regression analysis and after adjusting for BMI, insulin resistance presented by HOMA-IR, is found to be an independent predictor for adiponectin.

Hyperandrogenemia is one of the metabolic abnormalities often seen in PCOS. This was evident in our PCOS patients where the total testosterone concentration, AND, DHEA-S were significantly higher than in controls. Free androgen index was mostly evident and statistically significantly higher in the obese PCOS group. After adjusting for effects of BMI, SHGB was found to be an independent predictor of adiponectin levels.

Different trials have shown conflicting results of the relationship between adiponectin and androgen levels. Ardawi *et al.* have found negative associations between adiponectin, androstenedione, DHEAS, and a positive correlation between serum testosterone and SHBG (24). Vrbikova *et al.* found a positive correlation between the adiponectin and testosterone levels, BMI, and IR did not influence this relationship (25). Escobar-Morreale *et al.* found a negative correlation between serum adiponectin and testosterone, stating that hyperandrogenism and abdominal adiposity appear to be the major determinants of hypoadiponectinemia in PCOS (26). Administration of recombinant adiponectin decreases ovarian androstenedione level in Balb/C female mice. In addition to lower levels of the adiponectin, there is a decrease in ADIPOR1 and ADIPOR2 receptors in the theca of polycystic ovaries compared to normal ovaries. The indication that the adiponectin can lower androgen levels proposes its potential role as a mediator between metabolic and reproductive features in PCOS (27). Consistent with others, this study indicated that the observed hypoadiponectinemia in women with PCOS was related to hyperandrogenemia (24). Peloid treatment for osteoarthritis associated with obesity could improve adiponectin levels (28).

The major weakness of this study is that the women evaluated in the present study were recruited from the outpatient clinic of a tertiary care center and we did not achieve to recruit enough overweight/obese women for a control group. However, low adiponectin levels in obese subjects have been well documented.

Adiponectin may serve as a common biomarker that links obesity, IR, and altered metabolism among PCOS population. However, when studying the impact of obesity biomarkers in women with PCOS, overweight/obese and lean women should be evaluated separately. These results suggest that serum adiponectin levels may be involved in the pathogenesis of PCOS. Adipose tissues retain an important endocrinal, autocrine and paracrine structure, involved in complicated regulatory networks. Different adipocytokines may play important roles in the development and progression of IR-related syndrome and metabolic disorder in PCOS patients and pathogenesis of PCOS. Additional studies exploring the regulatory role of adipokines may be helpful to reveal the role of obesity in the etiology of PCOS.

**Conflict of interest**

The authors declare that they have no conflict of interest.

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