

# Systematic Review Article: Do Adiponectin and Nesfatin Levels Predict Polycystic Ovary Syndrome (PCOS)? An Update Systematic Review

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## ABSTRACT

**Background:** Contradictory findings regarding plasma levels of adiponectin and nesfatin-1 in patients with polycystic ovary syndrome (PCOS) have caused confusion among researchers. this update systematic review aimed to investigate the serum levels of adiponectin and nesfatin-1 in PCOS patients.

**Materials & Methods:** We systematically searched PubMed, Scopus, Google Scholar, Web of Science, Science Direct, Embase, and SID (an Iranian database) to identify relevant studies. In accordance with the PRISMA steps, the following keywords and their combinations were used: Adiponectin, Nesfatin-1, and PCOS.

**Results:** A total of 28 high-quality articles were identified, of which 23 were related to adiponectin (Four reported no significant association and 19 reported a negative and significant association with PCOS) and 5 articles were related to Nesfatin-1 (4 reported a negative and significant association and one reported no association).

**Conclusion:** This study demonstrated that levels of adiponectin and nesfatin-1 hormones may be appropriate predictors of PCOS.

## Introduction

Adipose tissue releases different hormones, cytokine, and various adipocytes such as leptin, nesfatin-1, adiponectin, orexin, etc. Nesfatin-1 and adiponectin are protein hormones secreted by adipose tissue (1-3). During the pregnancy, the placenta also produces these two hormones(4, 5). Nesfatin-1 and adiponectin also play a role in modulation, differentiation, and angiogenesis of

the placenta (e.g. in embryo implantation and embryo-maternal relations during pregnancy) (1, 2, 6). Various studies reported that patients with polycystic ovary syndrome (PCOS) can change plasma levels of adiponectin, including increased levels of vistaphine, leptin, and chemerin. Moreover, it's well documented that adiponectin dysfunction causes disturbances in the fertility system and hyperandrogenism(7, 8).

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Reduced serum levels of adiponectin and nesfatin-1 hormones in patients with PCOS is associated with increased levels of cholesterol, triglyceride, glucose, diastolic blood pressure, blood androgen, metabolic syndrome, and obesity(9, 10). Besides, these patients are at enhanced risk of cardiovascular diseases (CVDs)(11, 12). On the other hand, decreased levels of adiponectin and nesfatin-1 are associated with increased insulin resistance and elevated risk of type 2 diabetes (T2D) in patients with PCOS(13). In 2019, a review article(9) similar to the present article was conducted in which the number of articles were reviewed quantitatively and also the quality of the articles reviewed in their study was not at a desirable level; On the other hand, after that article, some other studies have been done and it seems necessary to update the mentioned article in order to be able to provide more logical reasons and review more up-to-date articles on the role of adiponectin and nesfatin- 1 commented on polycystic ovary syndrome. Also, the reduced release of nesfatin-1 and adiponectin causes ovulation disorders and increased infertility. PCOS is the main cause of approximately 75% of infertility due to anovulation. Considering the importance of PCOS and its pathophysiological diagnosis as well as contradictory findings regarding plasma levels of adiponectin and nesfatin-1 in patients with PCOS, the current systematic review aimed to investigate the serum levels of adiponectin and nesfatin-1 in PCOS patients. Besides, it worth noting that this disease contains a high financial burden for both health systems and families.

## Materials and Methods

### Study design

We systematically searched PubMed, Scopus, Google Scholar, Web of Science, Science Direct, Embase, and SID (an Iranian database) to identify relevant studies published from 2000 to 2019. The study process was performed

following the PRISMA steps (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

### Inclusion and exclusion criteria

The inclusion criteria included studies on women of reproductive age with PCOS, and no history of background diseases such as diabetes, blood pressure, which were published from 2000 to 2019. Exclusion criteria included lack of access to the full text of articles, studies presented at conferences, repeated studies, and studies with low quality based on the STROBE (Strengthening the reporting of observational studies in epidemiology) and CASP (critical Appraisal skills Programs) criteria.

### Quality Assessment

The quality of the articles was assessed based on the level of adherence to the STROBE checklist. It contains 22 items that should be observed. One point was given if the item met the proposed criteria and zero point if not met. Articles with less than 20% of the total score (i.e. <15.5) were categorized as of low quality. The CASP checklist was used for assessing the quality of systematic review and meta-analysis studies. This 11-item checklist is designed by the JAMA group. One point was given if the item met the proposed criteria and zero point if not met. The total score ranges from zero to 18. Articles with a score of 13 and more were categorized as of "good quality", 6 to 12 as "moderate quality", and less than 6 as of "poor quality"(14).

### Study Selection

Two researchers independently appraised the quality of all articles. In case of a disagreement, a consensus was reached through discussion.

### Tools

Articles that met the inclusion criteria were selected. The necessary information (e.g.

publication year, first author, study design, sample size, and final results) were extracted.

## Results

Initially, a total of 468 articles were identified, of which 20 met inclusion criteria (two cohort studies, 16 case-control studies, one cross-sectional, and a meta-analysis) (Figure 1).

Figure 1 Study selection process

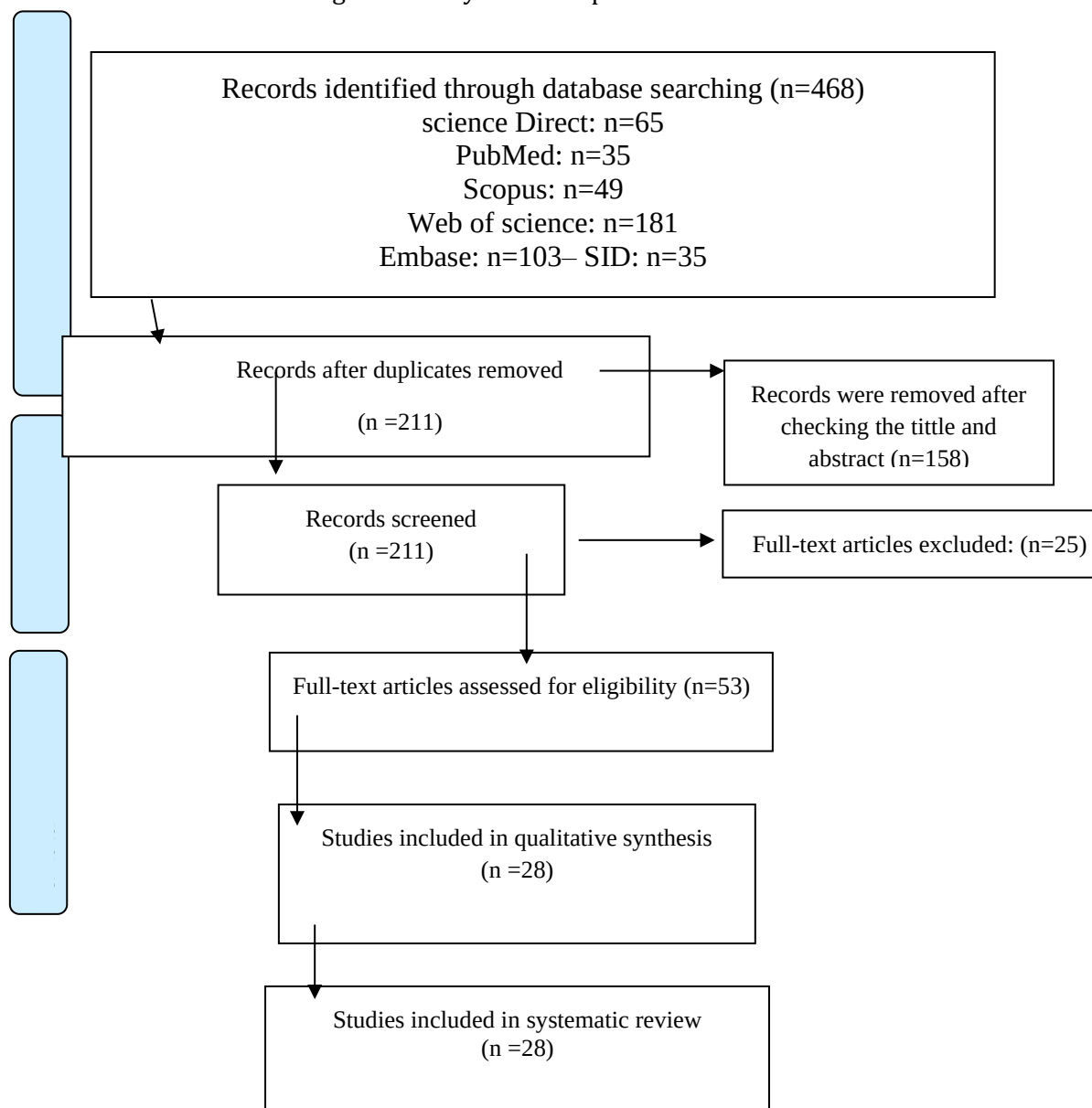


Figure 1. Study selection process

All identified articles were of good quality (Table 1).

**Table 1.** Quality Assessment of Articles

| First author<br>(year)                | check list | Title | Abstract | Introduction | method | Results | Discussion | Overall<br>score | Article<br>quality |
|---------------------------------------|------------|-------|----------|--------------|--------|---------|------------|------------------|--------------------|
| Toulis (2009)                         | CASP       | 1     | 1        | 2            | 8      | 5       | 4          | 21               | Good               |
| Panidis(2003)                         | STROBE     | 1     | 1        | 2            | 9      | 4       | 5          | 22               | Good               |
| Ducluzeau(2003)                       | STROBE     | 1     | 1        | 2            | 6      | 5       | 5          | 20               | Good               |
| Artimani (2016)                       | STROBE     | 1     | 1        | 2            | 8      | 8       | 4          | 24               | Good               |
| Orio (2003)                           | STROBE     | 1     | 1        | 1            | 9      | 5       | 5          | 22               | Good               |
| Spranger (2004)                       | STROBE     | 1     | 1        | 2            | 12     | 9       | 3          | 24               | Good               |
| Carmania(2005)                        | STROBE     | 1     | 1        | 2            | 10     | 10      | 3          | 27               | Good               |
| Ardawi (2005)                         | STROBE     | 1     | 1        | 1            | 12     | 10      | 4          | 29               | Good               |
| Escobar-<br>Morreale(2006)            | STROBE     | 1     | 1        | 2            | 9      | 7       | 5          | 25               | Good               |
| Gulcelik (2006)                       | STROBE     | 1     | 1        | 1            | 8      | 9       | 3          | 23               | Good               |
| Aroda (2008)                          | STROBE     | 1     | 1        | 2            | 10     | 8       | 4          | 26               | Good               |
| Bik (2007)                            | STROBE     | 1     | 1        | 2            | 13     | 11      | 3          | 31               | Good               |
| Katsikis (2009)                       | STROBE     | 1     | 1        | 2            | 7      | 9       | 3          | 24               | Good               |
| Olszanecka-<br>Glinianowicz<br>(2011) | STROBE     | 1     | 1        | 2            | 12     | 11      | 3          | 30               | Good               |
| Mazloomi (2012)                       | STROBE     | 1     | 1        | 2            | 13     | 11      | 4          | 32               | Good               |
| Comim (2013)                          | STROBE     | 1     | 1        | 2            | 7      | 9       | 4          | 24               | Good               |
| Yilmaz (2009)                         | STROBE     | 1     | 1        | 1            | 7      | 11      | 4          | 25               | Good               |
| Deniz (2012)                          | STROBE     | 1     | 1        | 2            | 8      | 9       | 4          | 25               | Good               |
| Ademoglu<br>(2014)                    | STROBE     | 1     | 1        | 1            | 9      | 9       | 3          | 24               | Good               |
| Binnetoğlu<br>(2014)                  | STROBE     | 1     | 1        | 2            | 13     | 10      | 3          | 30               | Good               |
| Khosrowbeygi<br>(2017)                | STROBE     | 1     | 1        | 2            | 11     | 10      | 3          | 28               | Good               |
| Alfaqih (2018)                        | STROBE     | 1     | 1        | 2            | 12     | 11      | 3          | 28               | Good               |
| Baldani (2019)                        | STROBE     | 1     | 1        | 2            | 13     | 10      | 3          | 30               | Good               |
| Bannigida<br>(2020)                   | STROBE     | 1     | 1        | 2            | 13     | 9       | 4          | 30               | Good               |
| Xianchang<br>(2017)                   | STROBE     | 1     | 1        | 2            | 13     | 10      | 3          | 30               | Good               |
| Cardoso (2020)                        | STROBE     | 1     | 1        | 2            | 13     | 10      | 3          | 30               | Good               |
| Shorakae (2018)                       | STROBE     | 1     | 1        | 2            | 12     | 11      | 3          | 30               | Good               |
| Alp (2015)                            | STROBE     | 1     | 1        | 2            | 13     | 10      | 3          | 30               | Good               |
| Ding (2020)                           | STROBE     | 1     | 1        | 2            | 13     | 10      | 3          | 30               | Good               |

Of 28 articles that met the inclusion criteria, 17 were systematic reviews on adiponectin and 3 on nesfatin-1.

### PCOS and Adiponectin

24 studies were on the association between adiponectin and PCOS, which have reported contradicting results. So that most studies reported a negative and significant association, and few reported no significant association. Five studies reported no association between serum level of adiponectin and PCOS.

For example, Panidis et al. (2003)(15) who studied serum levels of Adiponectin insulin LH, FSH, androgen, prolactin, and 17-hydroxyprogesterone of 85 Greek women (35 were suffering from PCOS with a BMI>25, 35 with a BMI<25, and 15 subjects without Hyperandrogenism in the control group).

They reported that the serum level of adiponectin was lower in obese people who were suffering from PCOS compared to the other two groups; but there was no association between serum adiponectin and PCOS levels in the other two groups. Ducluzeau et al. (2003)(16) investigated two groups of women (10 in the control group and 16 in the PCOS group), who were matched for weight. They reported that, in the control group, the serum level of adiponectin was  $6.3 \pm 13.6$  ng/ml; while the level of hormone among those with and without insulin resistance was  $3 \pm 6.5$  and  $2.9 \pm 8.6$  ng/ml, respectively, which there was no association between serum level of adiponectin and PCOS, but overweight subjects had lower levels of adiponectin.

Orio et al. (2003)(17) conducted a study on 69 women with PCOS (30 with normal weight and 30 obese) and 60 healthy women (30 with normal weight and 30 obese). They reported that the serum level of adiponectin for overweight subjects with PCOS was  $21.5 \pm 2.6$  ng/ml, for those with a normal weight  $35.6 \pm 2.5$  ng/ml, in non-PCOS obese subjects  $17.1 \pm 12.5$

ng/ml, in subjects with normal weight and no PCOS  $29.7 \pm 2.8$  ng/ml.

Also, they reported no association between serum levels of adiponectin in patients with PCOS and healthy subjects with the same weight, but serum levels of adiponectin were inversely associated with BMI; and in healthy obese subjects with PCOS, the serum level of adiponectin was lower than in healthy lean subjects with PCOS.

Spranger et al. (2004)(18) conducted a study on 62 women with PCOS and 35 healthy German women, participants were matched for body mass index (BMI), and reported no association between serum levels of adiponectin and PCOS levels in both groups.

Another article(19) (Khosrowbeygi et.al in 2017) aimed at serum levels of homocysteine, adiponectin and uric acid in gestational diabetes mellitus compared to normal pregnancy; In this study, 60 women (two groups of 30 women with gestational diabetes and healthy women) showed that there is no association between adiponectin and PCOS and this hormone cannot play a role in predicting PCOS.

Nineteen studies reported a significant negative association between serum levels of adiponectin and PCOS. Carmania et al. (2005)(20) examined 53 women with PCOS and 45 healthy women, who were matched for weight and age, and measured their serum levels of leptin, adiponectin, and resistin.

After matching for BMI, those suffering from PCOS had lower levels of adiponectin compared to their healthy counterparts. Ardawi et al. (2005)(21) investigated 45 obese women (BMI>30) with PCOS and 45 women with normal weight (BMI<25) with PCOS and 45 subjects with normal and no PCOS, and 45 obese subjects with no PCOS.

They reported that hypoadiponectin was a symptom of adiponectin in obese and lean subjects with PCOS compared to the controls, and it was not associated with weight.

Escobar-Morreale et al. (2006)(22), who aimed to investigate the serum level of adiponectin of 76 healthy women and 40 subjects without hyperandrogenism, reported that serum level of adiponectin in those with and without PCOS was  $5.3 \pm 1.9$  and  $5.3 \pm 1.9$  ng/ml.  $8.11 \pm 5.5$  ng/ml, respectively, which is a symptom of hypoadiponectin in those with PCOS compared to the controls. In those with PCOS, the hypoadiponectin was associated with hyperandrogenism, fat spread, insulin resistance, and beta-cell function, but it was not associated with obesity level.

In the case-control study conducted by Gulcelik et al. (2006)(23), which investigated 47 patients with PCOS and 23 healthy individuals as controls, who were matched for age and BMI, the authors reported no difference in the adiponectin level of the two groups, but they showed that hyperandrogenism, abdominal obesity, and increased insulin resistance were associated with adiponectin reduction. Increased insulin resistance and reduced adiponectin were associated with an enhanced risk of metabolic disorder and PCOS.

Bik et al. (2007) (24) investigated 20 obese women with PCOS, 37 non-obese women, and 45 healthy lean women aged 20 to 48 years, who were matched for age. They reported that in those with PCOS, the level of adiponectin was decreased with increasing the level of testosterone and ghrelin. They also reported that adiponectin was negatively associated with free androgen index testosterone levels, cholesterol and triglycerides, glucose levels, diastolic blood pressure, and concluded that adiponectin reduction was a symptom for the spread of metabolic syndrome or metabolic disorder in lean women with PCOS.

Also, Aroda et al. (2008)(25) examined glucose resistance, insulin activity, and circulation of adiponectin levels of 31 overweight and obese women with PCOS and 6 subjects in the control group, who were matched for BMI, and reported

that serum level of adiponectin in the PCOS group was  $9.9.5 \pm 0.77$  ng/ml and in the control, group was  $17.4 \pm 1.0$  ng/ml. They also reported that these individuals experienced decreased levels of serum adiponectin, particularly its high-molecular-weight.

In a meta-analysis conducted in 2009, Toulis et al.(26). reviewed 21 studies and reported that serum levels of adiponectin were lower in people with PCOS than controls, possibly associated with insulin resistance.

They also reported that hormones released by adipose tissues in obese people and those with high BMI are lower than non-obese people with PCOS. Katsikis et al. (2009)(27) examined 100 normal-weight women with PCOS who were divided into four groups based on PCOS phenotype and 25 healthy subjects in the control group. Subjects were matched for age and BMI. They also reported a significant decrease in serum levels of adiponectin in patients with severe PCOS and with chronic anovulation and hyperandrogenism compared to the control group, those with mild PCOS or with ovulation. Yilmaz et al. (2009)(28) examined 76 patients with PCOS (36 obese women and 40 non-obese women) and 42 healthy women. They investigated the levels of resistin, adiponectin, LH, and FSH and found that those who suffer from PCOS experience reduced levels of adiponectin and increased levels of resistin and hemostasis model index compared to their healthy counterparts.

Olszanecka - Glinianowicz (2011)(29) examined adiponectin, insulin-resistant resistin, and hyperandrogenism symptoms in 41 women with PCOS (22 lean and 19 obese) and 16 healthy lean women, and reported that adiponectin levels in obese women with PCOS were lower than lean women with PCOS, and serum levels of adiponectin in obese women with PCOS was  $10.8 \pm 8.3$  ng/ml and in lean women with PCOS was  $21.0 \pm 15.1$  ng/ml and in the control group it was  $26.7 \pm 12.5$  ng/ml. they also found no

significant association between serum level of adiponectin and LH and FSH.

Mazloomi et al. (2012) found that decreased vitamin D level is the cause of PCOS, probably through influencing BMI. In a case-control study, Comim et al.(2013)(30). investigated the adiponectin expression of 9 women without PCOS and 16 women with PCOS and compared its receptor expression in the ovaries of healthy women and those with PCOS.

They reported that adiponectin expression disorder and its receptor play a significant role in hyperandrogenism in those who suffer from PCOS. Artimani et al. (2016)(31) investigated receptor gene expression and granulosa cell adiponectin levels of 40 women without PCOS and 40 women with PCOS, and reported that the expression of adiponectin in people with PCOS is lower than their healthy counterparts. They also found a direct association between the expression of adiponectin receptors and LH and FSH receptors, but by reducing the level of adiponectin and its receptors, the number of gonadotropin receptors also decreases.

The study by Alfaqih et al. (2018) was conducted with the participation of 154 women with polycystic ovary syndrome with the aim of assessing the level of Adiponectin in women with PCOS; The study found that PCOS was inversely related to Adiponectin levels; Serum levels of Adiponectin in women with PCOS ( $6.582 \pm 0.2871 \mu\text{g/mL}$ ) were significantly lower ( $P = 0.0064$ ) than healthy women ( $7.916 \pm 0.3970 \mu\text{g/mL}$ )(32).

A study by Baldani et al. In 2019 aimed to compare the serum levels of leptin, adiponectin, resistin and ghrelin in women with PCOS ( $n=151$ ) and healthy women ( $n=95$ ). In this study, the researchers showed that serum adiponectin levels in women with PCOS were significantly lower ( $P<.001$ ) than healthy women, and that serum adiponectin levels were a strong predictor of the diagnosis of women with PCOS(33).

In a 2020 study by Bannigida et al., Serum visfatin and adiponectin-markers were performed in women with polycystic ovarian syndrome. In this study, 100 women with PCOS (50 obese women and 50 non-obese women) were compared in terms of serum visfatin and adiponectin levels. The results showed that the amount of adiponectin in obese women ( $10.79 \pm 0.71$ ) was significantly lower than non-obese women ( $13.84 \pm 0.61$ ) ( $p <.001$ ); They concluded that adiponectin levels were inversely related to PCOS(34).

A study was conducted by Xianchang et al. (2017) with the participation of 197 women with PCOS and 192 healthy women. This study was performed with the aim of linking adiponectin with PCOS.

Women with PCOS were divided into two groups (body mass index less than 25 and mass index more than 25) and adiponectin levels were measured in healthy women and women with PCOS (both groups). Finally, the researchers reported that adiponectin levels were significantly lower in women with PCOS than in healthy women( $p <.001$ ); Also, adiponectin levels in obese women with PCOS are significantly lower than non-obese women ( $p <.001$ ). Finally, they concluded that low levels of adiponectin have a strong and significant relationship in predicting PCOS(35).

A study by Cardoso et al. (2020) aimed to evaluate the serum level of adiponectin in women with PCOS. In this study, 120 healthy women (two equal groups) with PCOS participated and were divided into three groups based on body fat percentage (22-27%, 27-32% and 32-37%). Serum adiponectin levels were measured and compared in different groups. The results reported by them indicated that serum adiponectin levels were different between the two groups and that women with PCOS had lower levels of adiponectin. Also, with increasing fat percentage, the amount of this hormone decreases. Finally, it was stated that

decreased serum adiponectin levels are a good marker in the diagnosis of PCOS(36).

A study by Shorakae et al. (2018) aimed to evaluate the serum level of adiponectin in women with PCOS. This study was performed in the presence of 64 women with PCOS and 22 non-PCOS women and their serum adiponectin levels were measured and compared. Finally, the researchers stated that serum adiponectin levels in women with PCOS were significantly lower than in non-PCOS women ( $p=0.047$ ) and that low levels of adiponectin could be a predictor of PCOS (37).

### Nesfatin-1 in PCOS

Five articles on the role of nesfatin-1 in PCOS were identified, which showed conflicting results; Deniz et al. (2012)(38) investigated 30 women with PCOS and 30 control women, who were matched for age and BMI. They measured the levels of nesfatin-1, fasting blood sugar, insulin levels, and homeostasis model index, and reported that the level of nesfatin-1 in patients with and without PCOS was  $88.0 \pm 36.0$  and  $22.2 \pm 14.1$  ng/ml, respectively; they also found a significant reduction in the serum level of nesfatin-1 in patients with PCOS compared to their healthy counterparts. Although, in patients with PCOS, gonadotropin levels and androgen concentrations were increased. Ademoglu et al. (2014)(39) measured anthropometric, hormonal indices, and nesfatin-1 of 55 patients with PCOS and 28 age-matched healthy women. They reported that in patients with and without PCOS the level of nesfatin-1 was  $371.43 \pm 2.5$  and  $275.55 \pm 1.74$  pips/ml, respectively, which indicates the increased level of nesfatin-1 in patients with PCOS compared to their healthy counterparts.

Also, there was a significant association between serum levels of nesfatin-1 and BMI. However, Binnetoğlu et al. (2014)(40) investigated 37 women with PCOS and 28 healthy women and reported no association between serum levels of

nesfatin-1 and PCOS. Also, they reported no association between glucose metabolism and insulin resistance in patients with PCOS.

In the study of Alp et al. (2015), which was conducted to assess the level of Nesfatin-1 in women with PCOS, 55 women with PCOS and 35 healthy women were included in the study and their levels of Nesfatin-1 were measured and compared. The results showed that the amount of Nesfatin-1 in women with PCOS ( $2.29 \pm 0.558$ ) was significantly lower than healthy women ( $2.43 \pm 0.846$ ) ( $p=0.033$ ). The results of their study suggest that a decrease in Nesfatin-1 levels may be a good marker in the diagnosis of women with PCOS(41).

In a study by Ding et al. (2020) that aimed at the effects of the hormone Nesfatin-1 in women with PCOS. In this study, Nesfatin-1 levels of 30 women (two equal groups) with PCOS and healthy were measured and compared. The results showed that the level of Nesfatin-1 in women with PCOS ( $199.3 \pm 35.3524$ ) was significantly lower than healthy women ( $133.1 \pm 40.4085$ ) ( $p = 0.0266$ ). The researchers concluded that a decrease in Nesfatin-1 levels could be a good marker for women with PCOS(42).

### Discussion

PCOS is a common endocrine disease that affects 5 to 10% of women in reproductive age all around the world (43).

It's a heterogeneous and genetically complex disorder characterized by menstrual irregularities, clinical and biochemical manifestations of hyperandrogenism, and polycystic ovaries(44, 45). The PCOS causes infertility and because of affecting the physiology and metabolism of the body is recognized as a metabolic syndrome with abnormalities such as dyslipidemia, obesity, and hypertension(46). This syndrome is associated with an enhanced risk of T2D, CVDs, and endometrial and breast cancer in the long-term.

Nesfatin-1 and adiponectin play a role in regulating proliferation, differentiation, and angiogenesis of the placenta.

Therefore, it has a crucial role in embryo implantation and fetal-maternal relationship during pregnancy. According to the evidence, PCOS can change serum levels of adiponectin and Nesfatin-1. Several studies reported that these hormones cause PCOS and increased risk of T2D (47, 48).

Concerning the association between adiponectin and PCOS, based on the findings, those who suffer from PCOS have lower levels of adiponectin compared to others. Yamucci et al. (2002) (49) argued that adiponectin is associated with increased insulin sensitivity. Besides, they reported that through decreasing the activation of AMPK (adenosine monophosphat-activated protein kinase) in the liver, adiponectin causes metabolic disorders, increased insulin resistance, and increased weight, which is common in PCOS patients.

Another 2003 study by Yamuchi et al (50). Found that lower adiponectin levels were associated with lower fatty acid fuels, and that energy consumption led to insulin resistance and obesity in these individuals.

The results also showed that those who suffer from PCOS have increased serum levels of nesfatin-1, indicating that defects in nesfatin-1 receptors or post-receptor signals cause increased resistance to nesfatin-1 and its increased blood levels in patients with PCOS, which in turn results in increased levels of  $\alpha$ -MSH oxytocin and consequently increased levels of Corticotropin-releasing hormone. In turn, increased corticotropin-releasing hormone is associated with increased adrenocorticotrophic hormone and enhanced levels of cortisol and adipose tissues, which in turn causes a compensatory increase in nesfatin-1 and, ultimately, anovulation in people with PCOS (51).

## Conclusion

As evidenced in the literature, findings concerning the association between serum levels of adiponectin and nesfatin-1 with PCOS are contradicting, but most studies found a negative and significant association between serum levels of adiponectin and PCOS. Concerning the nesfatin-1, studies have reported quite different results and the evidence are not sufficient to conclude.

## Limitations of the Study

As studies with positive results have a higher chance of publication, publication bias is unavoidable. Also, no similar study was performed in Iran. Another important limitation was the lack of homogeneity of studies in terms of design and the type of variables.

## Suggestions for Future Studies

PCOS and its consequent fertility reduction cause high psychological, physical, and financial burden for both families and health systems. Also, these hormones have an important role in various diseases of obstetrics and gynecology such as infertility. Hence, the authors recommend performing further studies on these issues on various population groups and different ethnicities, mainly to provide further information for developing a treatment.

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**Conflict of Interests:** None.

**Ethical Issues:** None.

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## Key Massage

1. Polycystic ovary syndrome has many causes
2. Adiponectin does not have the predictive power of polycystic ovary syndrome
3. Nesfatin does not have the predictive power of polycystic ovary syndrome

## References

- [1]SR Fazeli Daryasari., et al., The role of adiponectin in gestational diabetes mellitus, preeclampsia and obesity during pregnancy: A systematic review. *Iranian Journal of Endocrinology and Metabolism*. **2018**; 19(5): 370-83. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [2]F Pahlavan., et al., Role of Adiponectin Hormone in Fertility and Sterility: A Systematic Review. *The Iranian Journal of Obstetrics, Gynecology and Infertility*. **2018**; 21(5):97-107. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [3]N Mobaraki Asl., et al., Comparing the effectiveness of intravenous oxytocin versus rectal misoprostol in the management of third-stage of labour after second-trimester abortion. *International Journal of Women's Health and Reproduction Sciences*. **2016**; 4(4):181-4. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [4]T Angelone., et al. Nesfatin-1 as a novel cardiac peptide: identification, functional characterization, and protection against ischemia/reperfusion injury. *Cellular and molecular life sciences*. **2013**; 70(3):495-509. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [5]S Farzipour., et al., Relationship of maternal vitamin D level with premature rupture of fetal membranes. *The Iranian Journal of Obstetrics, Gynecology and Infertility*. **2020**; 23(1):33-9. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [6]R Darghani., et al., Effect of cell-free fetal DNA on spontaneous preterm labor. *Journal of advanced pharmaceutical technology & research*. **2019**; 10(3):117. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [7]E Dos Santos., et al. Adiponectin and leptin systems in human endometrium during window of implantation. *Fertility and sterility*. **2012**; 97(3):771-8. e1. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [8]S Abbasalizadeh., et al. Review of Constipation Treatment Methods with Emphasis on Laxative Foods. *Current Nutrition & Food Science*. **2020**; 16(5):675-88. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [9]N Hasanheyvadi., et al., Role of adiponectin and nsafatin\_1 hormone in polycystic ovary syndrome: systematic review. *The Iranian Journal of Obstetrics, Gynecology and Infertility*. **2020**; 23(4):75-88. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [10] ES Hashemi., et al., Expression of miR200a as a biomarker in women with preterm delivery. *The Iranian Journal of Obstetrics, Gynecology and Infertility*. **2019**; 22(7):39-46. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [11] Y Liu., et al., Examining the potential of developing and implementing use of adiponectin-targeted therapeutics for metabolic and cardiovascular diseases. *Frontiers in Endocrinology*. **2019**; 10:842. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [12] H Salehi Aali., et al., Diagnostic value of Transvaginal Ultrasonography in abnormal uterine bleeding compared with Dilatation and Curettage in perimenopausal women. *The Iranian Journal of Obstetrics, Gynecology and Infertility*. **2017**; 20(6):40-9. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [13] SP Palit., et al. A genetic analysis identifies a haplotype at adiponectin locus: Association with obesity and type 2 diabetes. *Scientific reports*. **2020**; 10(1):1-10. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [14] S Cuschieri., The STROBE guidelines. *Saudi journal of anaesthesia*. **2019**; 13(Suppl 1): S31. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [15] D Panidis., et al., Serum adiponectin levels in women with polycystic ovary syndrome.

Human reproduction. **2003**; 18(9):1790-6. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[16] P-H Ducluzeau., et al. Glucose-to-insulin ratio rather than sex hormone-binding globulin and adiponectin levels is the best predictor of insulin resistance in nonobese women with polycystic ovary syndrome. The Journal of Clinical Endocrinology & Metabolism. **2003**;88(8):3626-31. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[17] F Orio Jr., et al., Adiponectin levels in women with polycystic ovary syndrome. The Journal of Clinical Endocrinology & Metabolism. **2003** 88(6): 2619-23. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[18] J Spranger., et al. Adiponectin is independently associated with insulin sensitivity in women with polycystic ovary syndrome. Clinical endocrinology. **2004** 61(6):738-46. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[19] A Khosrowbeygi., H Ahmadvand., Serum levels of homocysteine, adiponectin and uric acid in gestational diabetes mellitus compared with normal pregnancy. The Iranian Journal of Obstetrics, Gynecology and Infertility. **2017** 19(38):13-23. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[20] E Carmina, et al., Evidence for altered adipocyte function in polycystic ovary syndrome. European Journal of Endocrinology. **2005** 152(3):389-94. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[21] MSM Ardawi., AA Rouzi., Plasma adiponectin and insulin resistance in women with polycystic ovary syndrome. Fertility and Sterility. **2005** 83(6):1708-16. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[22] H Escobar-Morreale., et al. Adiponectin and resistin in PCOS: a clinical, biochemical and molecular genetic study. Human reproduction. **2006** 21(9):2257-65. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[23] NE Gulcelik., et al., Adiponectin is an independent determinant of insulin resistance in women with polycystic ovary syndrome. Gynecological endocrinology. **2006** 22(9):511-5. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[24] W Bik., et al., The relationship between metabolic status and levels of adiponectin and ghrelin in lean women with polycystic ovary syndrome. Gynecological Endocrinology. **2007** 23(6):325-31. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[25] V Aroda., et al., Circulating and cellular adiponectin in polycystic ovary syndrome: relationship to glucose tolerance and insulin action. Fertility and sterility. **2008** 89(5):1200-8. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[26] KA Toulis., et al. Adiponectin levels in women with polycystic ovary syndrome: a systematic review and a meta-analysis. Human reproduction update. **2009** 15(3):297-307. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[27] I Katsikis., et al., Oligo-ovulation or anovulation and hyperandrogenemia contribute to the decreased serum adiponectin levels in normal-weight women with PCOS with obesity and insulin resistance. Fertility and Sterility. **2009** 91(4): e3. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[28] M Yilmaz., et al. Serum resistin and adiponectin levels in women with polycystic ovary syndrome. Gynecological Endocrinology. **2009** 25(4):246-52. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[29] M Olszanecka-Glinianowicz., et al., Serum adiponectin and resistin in relation to insulin resistance and markers of hyperandrogenism in lean and obese women with polycystic ovary syndrome. European Journal of Obstetrics & Gynecology and Reproductive Biology. **2011** 154(1):51-6. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[30] FV Comim., et al., Adiponectin and its receptors in the ovary: further evidence for a link between obesity and hyperandrogenism in

- polycystic ovary syndrome. *PloS one*. **2013** 8(11): e80416. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [31] T Artimani., et al. Downregulation of adiponectin system in granulosa cells and low levels of HMW adiponectin in PCOS. *Journal of assisted reproduction and genetics*. **2016** 33(1):101-10. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [32] MA Alfaqih., et al., Lower levels of serum adiponectin and the T allele of rs1501299 of the ADIPOQ gene are protective against polycystic ovarian syndrome in Jordan. *Korean journal of family medicine*. **2018** 39(2):108. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [33] DP Baldani., et al., Altered leptin, adiponectin, resistin and ghrelin secretion may represent an intrinsic polycystic ovary syndrome abnormality. *Gynecological Endocrinology*. **2019** 35(5):401-5. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [34] DM Bannigida., SB Nayak SB. Serum visfatin and adiponectin-markers in women with polycystic ovarian syndrome. *Archives of physiology and biochemistry*. **2020** 126(4):283-6. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [35] X Sun., et al., Family-based association study of rs17300539 and rs12495941 polymorphism in adiponectin gene and polycystic ovary syndrome in a Chinese population. *Medical science monitor: international medical journal of experimental and clinical research*. **2017** 23:78. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [36] NS Cardoso., et al. Polycystic ovary syndrome associated with increased adiposity interferes with serum levels of TNF-alpha and IL-6 differently from leptin and adiponectin. *Archives of Endocrinology and Metabolism*. **2020** 64(1):4-10. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [37] S Shorakae., et al. High-molecular-weight adiponectin is inversely associated with sympathetic activity in polycystic ovary syndrome. *Fertility and Sterility*. **2018** 109(3):532-9. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [38] R Deniz., et al. Nesfatin-1 and other hormone alterations in polycystic ovary syndrome. *Endocrine*. **2012** 42(3):694-9. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [39] EN Ademoglu., et al. Plasma nesfatin-1 levels are increased in patients with polycystic ovary syndrome. *Journal of endocrinological investigation*. **2014** 37(8):715-9. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [40] E BINNETOĞLU., et al. Plasma Levels of Nesfatin-1 in Patients with Polycystic Ovary Syndrome. *Acta Medica*. **2014** 30:201. [[Google Scholar](#)], [[Publisher](#)]
- [41] E Alp., et al., Nesfatin-1 levels and metabolic markers in polycystic ovary syndrome. *Gynecological Endocrinology*. **2015** 31(7):543-7. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [42] P Ding., et al. Effects of Nesfatin-1 and Wnt/ $\beta$ -Catenin Pathway on OGCs in PCOS. **2020**. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [43] X Zhao., et al., Exploration of the relationship between gut microbiota and polycystic ovary syndrome (PCOS): a review. *Geburtshilfe und Frauenheilkunde*. **2020** 80(2):161. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [44] M Bahri Khomami., et al. Increased maternal pregnancy complications in polycystic ovary syndrome appear to be independent of obesity—A systematic review, meta-analysis, and meta-regression. *Obesity Reviews*. **2019** 20(5):659-74. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]
- [45] M Haghdoost., et al., Frequency of Chlamydia trachomatis Infection in Spontaneous Abortion of Infertile Women During First Pregnancy Referred to Tabriz University of Medical Sciences by Nested PCR Method in 2015. *international Journal of Women's Health and Reproduction Sciences*.

**2019** 7(4):526-30. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[46] N Ajmal, et al., Polycystic ovary syndrome (PCOS) and genetic predisposition: A review article. European journal of obstetrics & gynecology and reproductive biology: X. **2019** 3:100060. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[47] MJ Khorchani, et al., The phytoestrogen, quercetin, in serum, uterus and ovary as a potential treatment for dehydroepiandrosterone-induced polycystic ovary syndrome in the rat. Reproduction, Fertility and Development. **2020** 32(3):313-21. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[48] C Yin, et al., Copeptin and Nesfatin-1 are interesting interrelated biomarkers playing a role in the pathogenesis of insulin resistance in

Chinese obese children. **2020**. 76(4):223-232 [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[49] T Yamauchi, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nature medicine. **2002** 8(11):1288-95. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[50] T Yamauchi, et al. Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. Journal of Biological Chemistry. **2003** 278(4):2461-8. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

[51] M Khalafi, ME Symonds, The impact of high-intensity interval training on inflammatory markers in metabolic disorders: A meta-analysis. Scandinavian Journal of Medicine & Science in Sports. **2020** 30(11):2020-36. [[Google Scholar](#)], [[Publisher](#)], [[Crossref](#)]

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