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# Preptin and Adropin Levels as New Predictor in Women with Polycystic Ovary Syndrome

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**Abstract**

**Background:** Polycystic ovary syndrome (PCOS) is the common disorder that affects between 6-10% women of reproductive age. It is characterized by androgen excess, ovulatory dysfunction and associated with several metabolic abnormalities, particularly impaired carbohydrate metabolism, insulin resista- nce (IR), obesity and dyslipidemia, which play an important role in the pathophysiology of polycystic ovary syndrome and in particular, negatively influence ovarian function and fertility. Preptin is peptide hormone cosecre- ted from pancreas cells along with insulin, considered to be an enhancer of insulin secretion. Adropin is a newly identified peptide hormone and is critically involved in metabolic homeostasis, insulin resistance, dyslipidemia and the control of fatty acid and glucose metabolism.
Preptin and adropin seem to be of great significance among the previous factors responsible for metabolic disorders. The aim of this study was to evaluate plasma levels of preptin and adropin in women with PCOS.
**Material and method:** A case- control study included thrifty women with polycystic ovary syndrome, diagnosed on the basis of Rotterdam criteria and 30 healthy women, as the control subjects with regular menstruation, having similar age and body mass index (BMI). Serum preptin and adropin levels were determined by ELISA. Hormonal and Biochemical measurements were also performed.
**Results:** Serum preptin level was significantly higher ($P < 0.01$) and serum adropin level was significantly lower ($P < 0.01$) in the polycystic ovary syndrome group. There is significant positive correlations between preptin level and hormonal and metabolic markers; while, there is significant negative correlations between adropin level and hormonal and metabolic markers were observed.
**Conclusion:** Preptin and adropin might be a novel predictors of polycystic ovary syndrome in the future.

**Keywords:** Preptin, Adropin, polycystic ovary syndrome.

## INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopa- thies in women of reproductive age. PCOS etiology is not yet fully understood [(1–3)]. PCOS is diagnosed (in accordance with the Rotterdam criteria), if two out of the following three findings are present: oligo-ovulation or oligomenorrhea, polycystic ovaries on ultrasound and clinical or biochemical hyperandrogenism [(1, 2, 4)]. Women with PCOS are at risk of endometrial cancer, cardiovascular disease, type 2 diabetes, and infertility, among others. Typical PCOS symptoms include fertility disorders, hirsutism, obesity, acne, oligomenorrhea, and emotional or psychological disorders. PCOS symptoms are significantly affect the lives of patients, and in particular their emotional and psychological state, self- perception, satisfaction with life and quality of life. It is represent the leading cause of female infertility [(5–7)].

Preptin is a peptide hormone of 34-amino acid co-secreted from theβ cells of pancreas along with insulin and pancreastatin [(8)]. Its precursor is Pro- IGF-II, which also produces insulin-like growth factor II (IGF-II). IGF-II is involved in metabolism, differentiation and the regulation of cell growth. Preptin is a physiological enhancer of insulin secretion induced by glucose. Recent studies have revealed that there is a potential association between preptin and insulin resistance in humans [(9)]. Adropin is a 76 amino acid polypeptide encoded by energy homeostasis associated gene (Enho) involved in the regulation of energy and glucose homeostasis, lipid metabolism and maintaining insulin sensitivity [(10, 11, 12)].

## MATERIAL AND METHODS

This case- control study was carried out in Fertility Center, Al-Sader Teaching Hospital, Al- Najef, Iraq, during the period from January to March 2018. Thirty patients with PCOS and 30 healthy women were participated in the study. Age and body mass index (BMI) of patients were matched with control. The informed consent was obtained from all participants. The diagnosis of patients with PCOS were confirmed using the Rotterdam criteria. Other endocrinopathies and any chronic diseases were excluded and all the patients had not been treated with ovulation induction medication, insulin sensitizers, or other drugs. BMI was calculated as the ratio of weight (Kg) to height squared ($m^2$). Blood pressure was measured with the patients sitting in a chair. The blood sample of patients were routinely obtained in the morning following an overnight fast on day 2 of menstrual cycle. Serum of all participants were separated and frozen at -80°C until assayed. The concentration of fasting serum preptin, adropin and free testosterone were determined by Sandwich ELISA kits (Human, USA). Serum follicle-stimulating hormone (FSH), luteinizing hormone (LH) and total testosterone were measured determined by immune- fluorescence technique (Vidas, Biomerieux, France). Insulin and SHBG were measured determined by electrochemiluminescence technique **(**Cobas e 411 analyzer, Roche, Germany). Serum fasting glucose and serum lipid profile (TC, TG, HDL-C and LDL-C) levels were measured by standard enzymatic methods. Insulin resistance index (HOMA-IR) was estimated as follows: HOMA-IR = fasting glucose (mmol/L) × fasting insulin (mU/L)/22.5. The patients were divided into two groups patients with insulin resistance and non-resistance polycystic ovary syndrome based on HOMA-IR levels. The cutoff point value of HOMA- IR is > 2.5 [(13)].

**Statistics analysis:** SPSS software (version 21.0, SPSS Inc, Chicago, IL,) was used for statistical analysis. Values were expressed as mean ± SD; the values were statistically evaluated using unpaired Student's t-test. A P- value < 0.05 was considered statistically significant.

## RESULTS

Patients and control clinical characteristics and biochemical markers were summarized in table (1). However, no significant difference in demographic characteristics (age and BMI) of patients when compared with control. The study shown that serum preptin levels were statistically significant higher ($P < 0.001$) in patients with PCOS as compared with control group. In other hand, the study was shown that serum adropin levels were significantly lower ($P < 0.001$) in patients with PCOS as compared with control group. The current study also revealed that PCOS patients had highly significant fasting glucose ($P < 0.01$), HOMA-IR ($P < 0.001$), TC ($P < 0.001$), TG ($P < 0.001$), LDL-C levels ($P < 0.001$), FSH ($P < 0.01$), LH ($P < 0.001$), LH-FSH ratio, free testosterone ($P < 0.001$), total testosterone ($P < 0.001$) and DHEA ($P < 0.01$), but lower HDL cholesterol levels ($P < 0.001$) and SHBG ($P < 0.001$) as compared with control.

Additionally, the study showed that the increase in serum preptin levels is positively correlated with fasting glucose, TC, TG,

HOMA-IR, FSH, LH, LH-FSH ratio, Total Testosterone, DHEA-S and SHBG, negatively correlated with HDL. In other hand, the increase in adropin levels is negatively correlated with fasting glucose, HOMA-IR, FSH, LH, LH-FSH ratio, total testosterone, DHEA-S and SHBG, but positively correlated with HDL. The correlations results were illustrated in table (2).

Insulin resistance (HOMA index > 2.5) was observed in 16 cases (53.33%) of PCOS patients. There were significant differences in insulin (P= 0.000) and preptin (P= 0.032) levels between PCOS patients with and without insulin resistance. While, there were no significant differences in the others biomarkers (table 3).

**Table (1): The clinical characteristics and the laboratory values of women with PCOS and controls.**

| Characteristic | PCOS (n = 30) | Control (n=30) | *P* value |
|---|---|---|---|
| Age (y) | 26.73 ± 5.35 | 29.38 ± 6.83 | 0.101 |
| SBP (mm/Hg) | 116.83 ± 2.67 | 114.1 ± 3.68 | 0.002 |
| DBP (mm/Hg) | 74.53 ± 4.59 | 72.1 ± 2.95 | 0.018 |
| BMI (kg/m$^2$) | 24.97 ±2.23 | 24.26 ± 3.53 | 0.358 |
| Fasting glucose (mmol/L) | 4.68 ± 0.47 | 4.34 ± 0.51 | 0.009 |
| HOMA-IR | 13.33 ± 2.22 | 5.71 ± 3.9 | 0.000 |
| TC (mg/dL) | 179.97 ± 20.81 | 116.03 ± 17.76 | 0.000 |
| TG (mg/dL) | 144.23 ± 18.87 | 97.43 ± 17.23 | 0.000 |
| HDL-C (mg/dL) | 42.90 ± 2.39 | 50.23 ± 4.99 | 0.000 |
| LDL-C (mg/dL) | 108.22 ± 20.72 | 46.61 ± 13.11 | 0.000 |
| FSH (mIU/mL) | 6.76 ± 1.7 | 5.44 ± 1.54 | 0.003 |
| LH (mIU/mL) | 12.92 ± 0.66 | 3.35 ± 1.21 | 0.000 |
| LH-FSH ratio | 2.05± 0.66 | 0.64 ± 0.28 | 0.000 |
| Free Testosterone (pmol/L) | 11.95 ± 1.76 | 2.62 ± 1.24 | 0.000 |
| Total Testosterone (ng/mL) | 2.86 ± 0.91 | 1.52 ± 0.31 | 0.000 |
| DHEAS (µg/dL) | 146.26 ± 6.69 | 129.0 ± 13.72 | 0.006 |
| SHBG (nmol/L) | 24.81 ± 6.22 | 46.98 ± 7.48 | 0.000 |
| Preptin (pg/mL) | 464.47 ± 78.95 | 307.64 ± 58.73 | 0.000 |
| Adropin (pg/mL) | 148.09 ± 14.02 | 238.98 ± 13.9 | 0.000 |

P- Value ≤ 0.05 = significant.

**Table 2: Preptin and adropin levels correlations with other biochemical markers.**

| Test | Preptin (pg/mL) | | Adropin (pg/mL) | |
|---|---|---|---|---|
| | r | P Value | r | P Value |
| Fasting glucose (mmol/L) | 0.241 | 0.064 | -0.360 | 0.000 |
| HOMA-IR | 0.714 | 0.000 | -0.776 | 0.000 |
| TC (mg/dL) | 0.719 | 0.000 | -0.862 | 0.000 |
| TG (mg/dL) | 0.679 | 0.000 | -0.778 | 0.000 |
| HDL-C (mg/dL) | - 0.579 | 0.000 | 0.632 | 0.001 |
| LDL-C (mg/dL) | 0.709 | 0.002 | -0.839 | 0.000 |
| FSH (mIU/mL) | 0.354 | 0.000 | -0.386 | 0.002 |
| LH (mIU/mL) | 0.72 | 0.000 | -0.917 | 0.000 |
| LH-FSH ratio | 0.634 | 0.000 | -0.776 | 0.000 |
| Free Testosterone (pmol/L) | 0.721 | 0.000 | -0.909 | 0.000 |
| Total Testosterone (ng/mL) | 0.570 | 0.000 | -0.686 | 0.000 |
| DHEAS (µg/dL) | 0.417 | 0.001 | -0.342 | 0.000 |
| SHBG (nmol/L) | 0.666 | 0.000 | -0.772 | 0.000 |
| Preptin (pg/mL) | 1.0 | - | - 0.673 | 0.000 |
| Adropin (pg/mL) | - 0.673 | 0.000 | 1.0 | - |

P- Value ≤ 0.05 = significant.

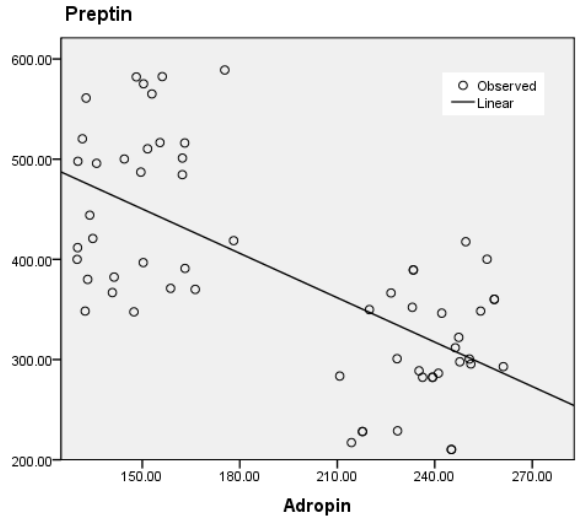


**Figure 1: Correlation between preptin levels with adropin in women with PCOS.**

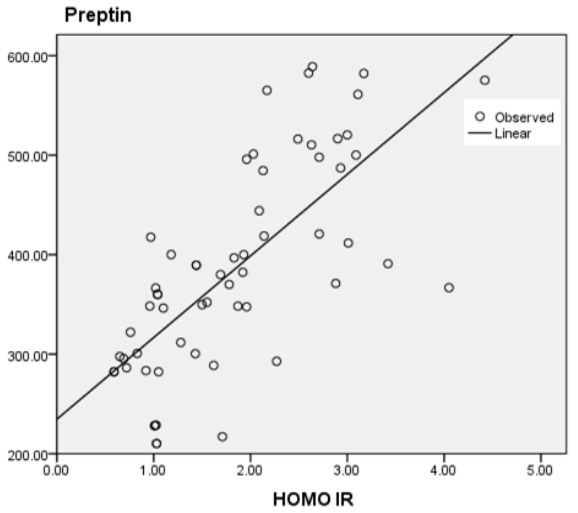


**Figure 2: Correlation between preptin levels with HOMA- IR in women with PCOS.**

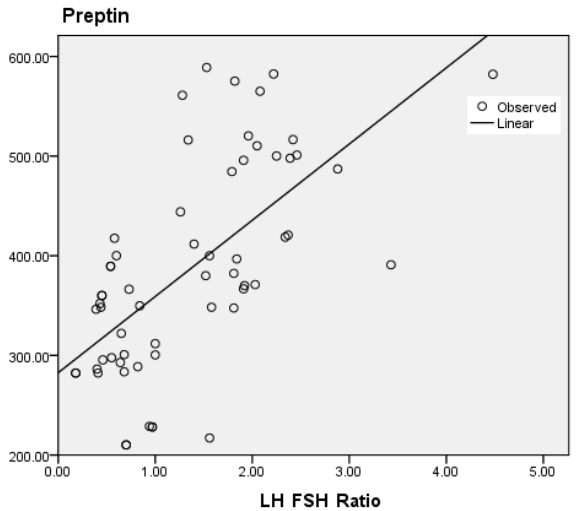


**Figure 3: Correlation between preptin levels with LH/FSH ratio in women with PCOS.**

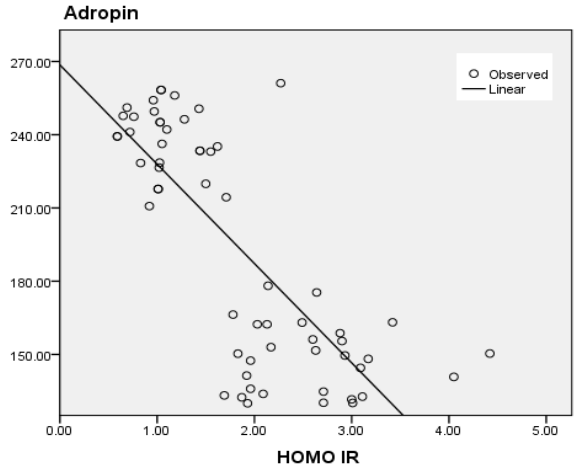


**Figure 4: Correlation between adropin levels with HOMA- IR ratio in women with PCOS.**

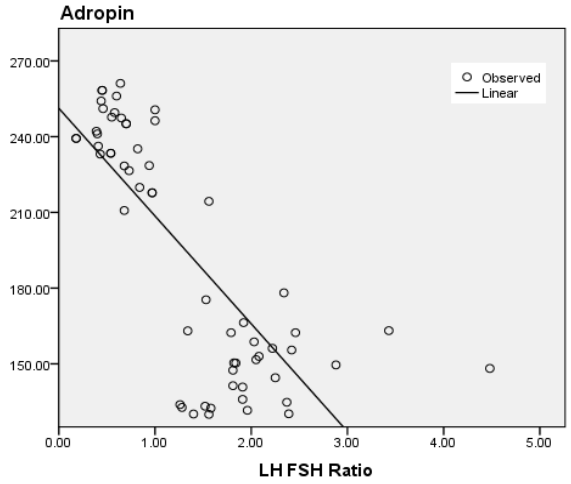


**Figure 5: Correlation between adropin levels with LH/FSH ratio in women with PCOS.**

**Table 3: The comparison of biochemical parameters between patients with insulin resistance and non-resistance polycystic ovary syndrome.**

| Characteristic | Non- insulin resistance patients (HOMO- IR <2.5) (No. = 14) | Insulin resistance patients (HOMA - IR >2.5) (No. = 16) | *P* value |
|---|---|---|---|
| Age (y) | 25.00 ± 4.69 | 28.25 ± 5.57 | 0.094 |
| SBP (mm/Hg) | 116.71± 2.97 | 116.94 ± 2.48 | 0.827 |
| DBP (mm/Hg) | 73.64 ± 4.81 | 75.31 ± 4.4 | 0.827 |
| BMI (kg/m$^2$) | 25.30±2.55 | 24.68± 1.94 | 0.463 |
| Fasting glucose (mmol/L) | 4.61 ± 0.59 | 4.75 ± 0.33 | 0.440 |
| Insulin (mU/L) | 11.91 ± 1.54 | 14.58 ± 1.98 | 0.000 |
| TC (mg/dL) | 178.36 ± 7.41 | 181.38 ± 28.02 | 0.684 |
| TG (mg/dL) | 143.86 ± 18.05 | 144.56 ± 20.15 | 0.920 |
| HDL-C (mg/dL) | 42.42 ± 1.39 | 43.31 ± 3.0 | 0.304 |
| LDL-C (mg/dL) | 107.16 ± 7.1 | 109.15 ± 28.0 | 0.787 |
| FSH (mIU/mL) | 7.06 ± 1.63 | 6.49 ± 1.76 | 0.365 |
| LH (mIU/mL) | 12. 32 ±1.39 | 13.45 ± 2.14 | 0.096 |
| LH-FSH ratio | 1.8± 0.34 | 2.27 ± 0.79 | 0.042 |
| Free Testosterone (pmol/L) | 11.43 ± 1.88 | 12.41 ± 1.57 | 0.134 |
| Total Testosterone (ng/mL) | 2.64± 0.86 | 3.05 ± 0.94 | 0.229 |
| DHEAS (µg/dL) | 137.71 ± 16.96 | 153.74± 36.17 | 0.127 |
| SHBG (nmol/L) | 27.52 ± 7.84 | 22.44 ± 4.53 | 0.046 |
| Preptin (pg/mL) | 432.19 ± 69.13 | 492.72 ± 78.0 | 0.032 |
| Adropin (pg/mL) | 149.25 ± 16.35 | 147.07 ± 13.17 | 0.683 |

## DISCUSSION:

PCOS is a severe clinical and public health issue, as it is related with a number of long term significant women health risks [2, 3]. Preptin and adropin new proteins are now surfacing as potential new biomarkers of PCOS due to their role in increase insulin secretion [14]. Preptin is a physiological enhancer of insulin secretion induced by glucose. There is a strong correlation between PCOS, insulin resistance, hyperinsulinemia and obesity and these get stronger with increasing body weight. Therefore, the relationship between preptin levels and BMI would be worth investigation [15]. In the scientific literature, there is a strong connection between preptin and adropin and PCOS physiopathology. Buchanan et al, in 2001, reported that glucose-mediated insulin secretion was increased by approximately 30 % in isolated, perfused pancreas of rat which were infused with preptin. Subsequently, the binding of anti- preptin antibodies to preptin, lead to decrease insulin secretion. In addition, serum preptin levels were reported to be significantly higher in patients with impaired glucose tolerance and diabetic mellitus types 2 as compared with healthy controls [16].

The present study revealed that fasting plasma preptin levels was highly significantly increased in PCOS patients as compared to healthy controls and another important finding of the present study that plasma preptin levels were positively correlated with HOMA-IR, indicating that there is a potential link between IR and preptin and suggesting that preptin may play a essential role in the pathogenesis of insulin resistance [9]. A systematic review and a meta-analysis study [17], and Yusuf O et al. [18], were reported identical results. Celik et al., reported that plasma preptin levels in patients with PCOS were statically higher as compared with patients without PCOS, suggesting that preptin is involved in the pathogenesis of PCOS [19]. This finding was in agreement with Agata et al., [20]. All of these findings led to conclude that PCOS is responsible for the elevation of plasma preptin levels in women with PCOS.

The current study revealed, there was significant decreased levels of adropin in women with PCOS group as compared to control, also adropin levels is negatively correlated with fasting glucose, HOMA-IR ,TC, TG, free testosterone, total testosterone, DHEA, preptin and LH-FSH ratio. Recent findings concerning diabetes mellitus and insulin resistance suggest that adropin peptide regulated carbohydrate metabolism and lipid in key insulin-targeted tissues [21- 23]. Additionally, lower adropin levels were associated with insulin resistance [24-26]. A clinical study revealed that serum adropin level was significantly lower in patients with type 2 diabetes mellitus than in those without diabetes. In women with PCOS, serum adropin level correlated negatively with triglycerides, LDL cholesterol, insulin resistance (HOMA-IR) and preptin, while positive correlations with HDL cholesterol [24]. Similarly, previous study revealed that serum adropin levels were lower in PCOS women than in the healthy control. The lower plasma adropin levels in PCOS patients in comparison to healthy population may be explained by carbo- hydrate intolerance present in both these diseases.

Additionally, in woman with PCOS, plasma adropin level correlated negatively with fasting serum glucose, TC, triglycerides, LDL cholesterol, VLDL, insulin resistance (HOMA-IR), LH/FSH ratio, free testosterone, DHEA and preptin [25].

In other hand, the current study was explored the role of LH/FSH ratio as an indicator for PCOS. This will be beneficial to physician for the better management of disease. Since results showed a highly significant elevation in LH/FSH ratio were found in PCOS group then comparing with control. Therefore, the LH-FSH ratio is a valuable diagnostic tool in evaluating PCOS women if preptin and adropin are not available. LH-FSH ratio of >1 may be used as a decision threshold. These results are also consistent with findings of Hsu et al. [27], and Hendrick et al., [28].

## CONCLUSIONS:

The results of the presented study showed that preptin levels were elevated in PCOS patients compared with control. Serum preptin levels were positively related with insulin resistant, LH/FSH ratio, PCOS status, but negatively with adropin. The current study results revealed that preptin may have a role in pathophysiological of PCOS. The findings of current study revealed that women with PCOS have low serum adropin levels that may contribute to the underlying pathogenesis of metabolic disturbances in PCOS. Additionally, plasma adropin level correlated negatively with fasting serum insulin levels, LH/FSH ratio, PCOS status, preptin, and HOMA-IR.

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