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EVALUATION OF ADROPIN AND ITS RELATIONSHIP WITH METABOLIC DISORDERS IN POLYCYSTIC OVARY SYNDROME

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Abstract

Background: Adropin is a hormone that has been connected with several inflammatory disorders and has also been linked to metabolic problems that constitute a fundamental component of polycystic ovarian syndrome (PCOS).

Aim: The objective of the current study was to assess the level of adropin in patients with polycystic ovarian syndrome (POS) in Mosul City and investigate the correlation between adropin and indicators of metabolic.

Study Design: A case-control study.

Methods: 110 women between the ages of 15 and 45 were split into two groups: 47 women with regular menstrual cycles, who were classified as non-PCOS (apparently healthy), and 63 women classified as PCOS (based on Rotterdam criteria). PCOS was diagnosed in patients attending Al-Batoul Teaching Hospital (Obstetrics and Gynecology) in Mosul City, Iraq, who presented with oligomenorrhea (irregular menstrual periods), hyperandrogenism, and polycystic ovaries (on the ultrasound).

Ten milliliters of venous blood were extracted from the women fasting all night. Clinical analyses were performed using the following methods: ELISA was used to measure the serum adropin level, metabolic factors which are fasting glucose, insulin, lipid profile, and standard formulas were used to calculate the IR indices (HOMA), (HOMA-%β), (HOMA-%S) and (TyG) were also estimated.

Results: it showed that adropin hormone levels were much lower in PCOS patients than in non-PCOS patients. Additionally, a significant increase in glucose, insulin, and the homeostasis model for insulin resistance (HOMA-IR), Triglyceride Glucose index (TyG), and lipid profile, also the results showed a decrease in the homeostasis model for β-cell function (HOMA-%β), the sensitivity of insulin (HOMA-%S) and there is a significant correlation between the adropin hormone with many indicators.

Conclusion: reduced levels of adropin were associated with Polycystic ovary syndrome and metabolic disorders. Therefore, it can be considered a new indicator and a promising tool for diagnosing initiating and developing Polycystic ovary syndrome.

Keywords: *Adropin; polycystic ovary syndrome; Insulin resistance; Triglyceride Glucose index*

Introduction:

The secreted peptide adropin is mostly expressed in the liver and brain and is encoded by the Energy

Homeostasis Associated (ENHO) gene[1]. It proved that adropin improves glucose homeostasis 2, energy balance, dyslipidemia, and obesity-related hyperinsulinemia.[2]. Adropin binds to three different membrane receptors to produce its biological effects [3]. These receptors appear to be in charge of different target tissue metabolic modulations[4]. Strong evidence suggests that adropin can improve cardiac function and coronary blood flow, lower serum triglyceride, total cholesterol, and low-density lipoprotein cholesterol levels, and increase high-density lipoprotein cholesterol levels[5].

Polycystic ovary syndrome (PCOS) is a relatively common endocrine-metabolic condition that has serious implications for the health of women, including infertility[7]. Hormonal abnormalities include insulin resistance (IR), hyperandrogenemia, and hyperinsulinemia[8]. Insulin resistance in ovarian tissue leads to altered metabolic signaling that favors hyperandrogenemia, which appears to be the fundamental cause of the clinical picture associated with (PCOS) [9]. Insulin appears to disrupt the hypothalamus-hypophysis-ovary axis in all of its components.[9-10]. Androgens can then cause IR again by raising free fatty acid levels and changing the structure and function of muscle tissue, which feeds the cycle of IR, hyperinsulinemia, and hyperandrogenemia[11]. Metabolic problems constitute a fundamental component of polycystic ovarian syndrome (PCOS), although not listed in the diagnostic criteria [12]. Adropin appears to be a major factor among the new probable causes of metabolic diseases. There is growing evidence that adropin has a role in polycystic ovarian syndrome (PCOS) and is strongly linked to several inflammatory disorders [13]. It also has a significant impact on controlling the biological activity and phenotype of immune cells, as well as the release of inflammatory cytokines, the precise mechanisms remain to be thoroughly and methodically understood [14].

Materials and methods

This research was approved and necessary permissions for data of the study by Mosul University /Ministry of Higher Education and Scientific Research, and Nineveh Health, the Iraqi Ministry of Health.in addition, this study has received ethical approval from the Medical Research (Research No. 2023015) Ethics Committee following the Helsinki Declaration. The study approval number and date on (716, 8 /1/2023).

The current study used a case-control methodology.

Venous blood samples (10 ml) were collected from the beginning of January 2023 to the end of April 2023 for the women overnight fasting. women (110) aged 15–45 years were divided into a non-PCOS (apparently healthy) group consisting of 47 women with regular menstrual cycles and a PCOS group consisting of 63 women, PCOS was diagnosed based on Rotterdam criteria [15], including women present with Oligomenorrhea (irregular menstrual periods), Hyperandrogenism and Polycystic ovaries (on the ultrasound) for patients attending Al-Batoul Teaching Hospital (Obstetrics and Gynecology), information was recorded according to the questionnaire paper.

Exclusion criteria: Women with diabetes mellitus, high blood pressure, liver diseases, and any other known case of chronic diseases were excluded from the present study, as well as PCOS Patients with previous medications.

Measurement demographic and biochemical parameters:

All Participants underwent a physical examination. Anthropometric measurements (weight, height, waist) were performed on all women. An automated equipment was used to take the participant's

blood pressure twice, systolic and diastolic, and average the results. The blood pressure was then tested after the individual had been sitting for at least five minutes.

BMI was calculated as the weight (kg) to height squared (m2) ratio.

Waist-to-height ratio (WHtR) was calculated as the ratio of waist circumference (cm) to height (cm).

Adropin and Insulin: they were measured by using an Enzyme-Linked Immunosorbent Assay (ELISA) kit from SUN LONG Biological Technology Co., Ltd kit (China). The evaluation was done according to the instructions provided by the manufacturer.

The concentration of **fasting glucose, triglyceride (TG),** and high-density lipoprotein-cholesterol **(HDL-C)** were estimated using a ready-made assay (kits) from the company (BIOLABS) and using enzymatic methods.

HOMA-IR= insulin (μU/ml) × glucose (m mol/L) / 22.5

HOMA-%S =1 / HOMA-IR

HOMA-β (%) = insulin (μU /ml) × 20 / (glucose (m mol/ L)-3.5)

Triglyceride Glucose (TyG) Index = In [T.G(mg/dl) × fasting glucose (mg/dl)] /2

Data Analysis: The data is shown as mean ± SE. The comparison between the arthritis group and the control group using the t-test. Pearson correlation coefficient (r) was applied to determine the relation between parameters based on linear regression analysis. P values ≤ 0.05 are considered significant.

Results

Baseline Anthropological Characteristics of The Study Participants

Table (1) displays basic clinical and anthropometric information on polycystic ovarian syndrome (PCOS) and control groups **(non-PCOS)**. The BMI, waist circumference, WHtR, systolic blood pressure (SBP), and diastolic blood pressure (DBP) of patients with polycystic ovarian syndrome were significantly greater at the level of significance (P ≤ 0.05) compared to the controls; however, the patients' ages for (PCOS) were lower than those of the control females.

Table 1. Basic clinical and anthropometric information on (PCOS) and control groups

Variables	non-PCOS (Mean ± SD)	PCOS Mean ± SD
No. of subjects F	47	63*
Age (years)	31.5 ±11.8	26.7 ± 9. 3*
BMI (kg/m2)	28. 9 ±8.7	33. 4 ±6. 8*
Waist circumference (cm)	93.5 ± 3.2	99.8 ± 6.5*
WHtR	0.55	0.68*
Smoking	No	No
SBP / DBP (mm Hg)	13.1 ± 1.4 / 8.3 ± 0.4	14.7 ± 1.3 / 9.1 ± 0.7*

*** Significant at the level (P ≤ 0.05)**

The Effect of Body Mass Index (BMI) on The Level of Adropin

The effect of the body mass index was studied as one of the methods used to determine obesity. The polycystic ovary syndrome (PCOS) and non-PCOS groups were divided into three groups based on the body mass index (BMI) value. As shown in Table (2), the results showed a significant decrease at the level of (P≤0.05) in the adropin level when the body mass index (BMI) is high, as the highest value of the adropin level was found in women of normal weight who had a

BMI (18 - 24.9 Kg\m²), as well as the lowest value of the adropin level in obese women who had a BMI (≥30Kg\m²).

The results in Table (2) also indicate that there is a significant decrease in the level of adropin in the blood serum of polycystic ovary syndrome patients at the level (P≤0.05) compared to its level in the non-PCOS group according to the body mass index.

Table 2. The effect of BMI on the level of adropin for PCOS and non-PCOS

Clinical Parameters	non-PCOS Mean ± SD	PCOS Mean ± SD
F.B.S(mg\dl)	77.6±8.3	110 ±11.1*
Insulin(µIU\ml)	6.7±1.5	9.6 ±3.1*
HOMA-IR	2.28±0.6	4.31±0.9*
HOMA-β	165.2±24.07	73.5±12.5*
HOMA-%S	0.43 ±0.13	0.23±0.05*
Triglyceride Glucose Index (TyG)	1.08±0.14	1.36±0.27*

BMI-Kg\m²	Adropin (ng\ml)	
	non-PCOS Mean ± SD	PCOS Mean ± SD
18-24.9	0.75 ± 0.19 a	0.52 ± 0.26* a
25-29.9	0.54 ± 0.09 b	0.31 ± 0.09 * b
≥30	0.32 ± 0.08 c	0.13 ± 0.07 *c
Total	0.53 ± 0.12	0.32 ± 0.14 *

*** Significant at the level (P ≤ 0.05)**

Markers of Glucose, Insulin Resistance, and Sensitivity for PCOS

Table (3) showed a significant increase in the concentration of markers (glucose, insulin, insulin resistance (HOMA-IR), and triglyceride glucose index (TyG), but a decrease in homeostasis model assessment for beta-cell function (HOMA- β) and (HOMA-%S) in serum patients with PCOS when compared to the control group at the level (P ≤ 0.05).

Table 3. Markers of glucose, insulin resistance, and sensitivity for PCOS and non-PCOS

Different letters vertically indicate a significant difference at the level (P ≤ 0.05)

***Horizontally, it indicates a significant difference at the level (P ≤ 0.05)**

Markers of Lipid Profile for PCOS

Table (4) showed a significant increase in the concentration of markers (TC, TG, LDL, VLDL, Non-HDL, and Atherogenic Index (AI), but a decrease in HDL in serum patients with PCOS when compared to a non-PCOS group at the level (P ≤ 0.05).

Table 4. Markers of lipid profile for PCOS and non-PCOS

Markers of lipid profile	non-PCOS Mean ± SD	PCOS Mean ± SD
TC (mg\dl)	148.7±27	190.3± 21*
TG (mg\dl)	85.7±15.2	116.3±16.4*
LDL (mg\dl)	81.1±19.5	132.9±22.4 *
HDL (mg\dl)	48.16±5.1	34.08±2.9 *
VLDL (mg\dl)	17.1±3.1	23.2±4.3*
Non -HDL (mg\dl)	96.1±18	156.2±21.9 *
Atherogenic Index (AI)	3.1±0.8	5.5±1.0 *

*** Significant at the level (P ≤ 0.05)**

Correlation between Adropin and Metabolic Factors for PCOS

Serum adropin was negatively correlated with adiposity-related parameters (BMI and WHtR) as well as blood pressure (SBP / DBP) at the level (P ≤ 0.05) and the results in Table (5) showed that adropin had a negative correlation with fasting glucose, insulin, (HOMA-IR), (TyG), TC, TG, Non-HDL, LDL, VLDL, and Atherogenic index. Also, adropin had a positive relationship with HDL, (HOMA-% β), and (HOMA-%S), in PCOS at the level (P ≤ 0.05).

Table 5. Correlation between adropin and Metabolic Factors for PCOS

Adropin	
Parameters	**PCOS (R-value)**
SBP / DBP (mm Hg)	- 0.835*
BMI-Kg\m²	- 0.842*
WHtR	- 0.515*
F.B.S(mg\dl)	- 0.5 02*
Insulin(µIU\ml)	- 0.518 *
HOMA-IR	- 0.4 14*
HOMA-β	+ 0.567*
Triglyceride Glucose Index (TyG)	0.307
HOMA-%S	+ 0.499*
TC (mg\dl)	- 0.521*
TG (mg\dl)	- 0.504*

HDL (mg\dl)	+ 0.811*
Non-HDL	- 0.853*
LDL-C (mg\dl)	- 0.542*
VLDL-C (mg\dl)	- 0.509*
Atherogenic index	- 0. 527*

* Significant at the level ($P \leq 0.05$)

Dissection

According to the study's findings, every patient with polycystic ovarian syndrome (PCOS) who underwent a baseline information evaluation had high values for, BMI, WHtR, waist circumference, and systolic and diastolic blood pressure, all of these were consistent with research [16-17]showing a link between the onset of PCOS and weight gain following puberty and abdominal obesity. Additionally, it has been demonstrated that obesity worsens the clinical side effects of polycystic ovary syndrome (PCOS), such as insulin resistance, hirsutism, and the frequency of infertility[18]. Notably, it has been demonstrated that PCOS symptoms resolve after bariatric surgery and obesity correction [16]. Also, each of the features of the syndrome (anovulation, androgen excess, and insulin resistance) is associated with hypertension in women [19]. Moreover, treatment for hypertension aims to treat these abnormalities and features [20]. An additional study found a link between PCOS and hypertension by the assumption that hyperlipidemia and IR have a role in the pathophysiologic features of hypertension in PCOS women [21].

The low level of adropin is due to an increase in risk factors associated with polycystic ovary syndrome, such as a decrease in the vasodilatory response resulting from adropin in patients[13], as with age, dysfunction occurs. In the vascular endothelium [22]. This is consistent with additional studies [23-24] showed that the low level of adropin is due to the pathophysiology of (PCOS) and the disturbance of hormones and metabolism, as a relationship was found between low adropin and hyperandrogen in the blood for (PCOS) through the hormone binding globulin (SHBG), a drop in adropin is also associated with the development of insulin resistance, which has a role in the syndrome [25-26].

In addition, [27], found that a decrease in the level of adropin was more evident in obese women with (PCOS), as a decrease in adropin was associated with a higher body mass index value in (PCOS)[28] indicated that a decrease in adropin may contribute to the metabolic disorders that appear in (PCOS), such as hyperlipidemia and insulin resistance (IR), which in turn are linked to other health problems such as high blood pressure, diabetes, and cardiovascular disease, which It indicates that there is an inverse relationship between adropin and the value of the body mass index, and this is consistent with what was shown by[29] (Radić et al., 2023).

The high concentration of glucose, insulin, insulin resistance, and (TyG) with low (HOMA-%S) (HOMA-β) in (PCOS) group is attributed to the fact that hyperinsulinemia and insulin resistance are associated with the hyperandrogenism that appears in polycystic ovary syndrome[30]. Insulin plays an important role in reproduction through its direct effect on the granulosa cells in the ovary and theca cells that regulate ovulation and generate steroid hormones in the ovaries. Thus, insulin resistance is associated with hyperandrogenism in (PCOS) [31,23] and the relationship of (PCOS)

with insulin resistance is also due to increased phosphorylation of insulin receptor proteins, which reduces the effectiveness of the enzyme tyrosine kinase, which works to secrete Excessive insulin [32]. This results in the appearance of numerous ovarian cysts and ovarian enlargement. Excess androgen also contributes to poor beta cell function in women with (PCOS)[11].

Dyslipidemia is one of the most common metabolic disorders in women with (PCOS)[33-34] and this is consistent with what is found in a high concentration of (TC), (TG),(LDL), (VLDL-C), and (Non-HDL), also, low (HDL) in (PCOS)group, the cause of lipid disturbance in polycystic ovary syndrome is due to hyperinsulinemia and hyperandrogenism, which stimulates an increase in lipolysis and the release of free fatty acids from fat cells into the blood circulation. An increase in free fatty acids in the liver leads to the secretion of (VLDL), which leads to High hypertriglyceridemia and (LDL) and reduced (HDL) [35]. Insulin resistance also stimulates lipolysis and gene expression of lipoprotein lipase and hepatic lipase [23]. An increase in the atherogenic index (AI) is observed in (PCOS)group and this is consistent with what was found[36], it is considered one of the useful indicators for evaluating the risk of cardiovascular disease in patients with (PCOS), especially patients who suffer from insulin resistance [37].

The relationships between adropin and indicators of glucose, insulin resistance, and sensitivity are because adropin can improve glucose metabolism and insulin sensitivity by inhibiting the production of inflammatory cytokines, and it also works to regulate carbohydrate and fat metabolism [14]. In addition, it may contribute to low serum adropin is associated with metabolic problems that appear in patients with polycystic ovary syndrome, such as insulin resistance and lipid disorders [23]. Also, the relationships between adropin and lipid indicators are because the level of adropin in the blood is affected by fat intake in women. Adropin affects fat metabolism, as it can reduce the levels of triglycerides and total cholesterol in the blood, it also works to regulate gene expression of lipoproteins in the liver and peroxisome proliferator-activated receptor gamma (PPARY) [27]. Cholesterol also inhibits (Enho mRNA), leading to a decrease in adropin production [38].

Conclusion

women patients (PCOS) a clear correlation between adropin hormone and Indicators of glucose and fat metabolism in the blood, as well as insulin resistance, abdominal obesity, and hypertension. reduced levels of adropin were associated with Polycystic ovary syndrome. Therefore, it can be considered a new indicator and a promising tool for diagnosing initiating and developing Polycystic ovary syndrome.

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Conflict of Interest

The authors have no conflicts of interest regarding the publication of this article.

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