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Original Research Article

Study Interplay between Adropin, Oxidative Stress, and Polycystic Ovarian Syndrome

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Abstract

This Study Interplay investigates evaluates and compares the relationship of Adropin with oxidative stress as a clinical predictor for the development of polycystic ovarian syndrome (PCOS). A clinical investigation was undertaken from January 2023 to the end of April 2023 for 63 women with PCOS diagnosed based on Rotterdam criteria, from the Al-Batoul Teaching Hospital (Obstetrics and Gynecology) in Mosul City/Iraq, as well as, 47 women with regular menstrual cycles as a non-PCOS group. Significant increases ($P \leq 0.05$) were in the Body mass index (BMI), Waist-to-height ratio (WHtR), systolic blood pressure (SBP), and diastolic blood pressure (DBP), in addition to total cholesterol (TC), triglycerides(TG), non-high-density lipoprotein(non-HDL), glucose, insulin, insulin resistance (HOMA-IR), peroxynitrite, malondialdehyde and the activity of peroxidase, but a significant decrease in HDL, vitamin C, vitamin E, glutathione, and the activity of the arylesterase in PCOS as compared to a non-PCOS group. Adropin levels were a significant decrease with getting older in all participants. Also, in PCOS patients compared to non-PCOS ($P \leq 0.05$). A negative correlation ($p \leq 0.05$) between Adropin levels and BMI, blood pressure, TC, TG, non-HDL, glucose, insulin, (HOMA-IR), and Malondialdehyde. In addition, a positive correlation with HDL in PCOS, which appears to be an Adropin level, may have a significant role in initiating and developing PCOS.

Keywords: Adropin, Insulin resistance, Obesity, Oxidative stress; Polycystic ovary syndrome

INTRODUCTION

The disorder known as polycystic ovarian syndrome (PCOS) is characterized by high androgen levels, ovulatory failure, and abnormal changes. The definition provided by the National Institutes of Health (NIH) is "hyperandrogenism with ovulatory dysfunction" in Women's reproductive stages) Livadas and Evanthia, 2013). PCOS is associated with environmental variables, such as obesity, and factors contributing to obesity (Barber et al., 2019). In general, PCOS is characterized by elevated levels of luteinizing hormone (LH), insufficient follicle-stimulating hormone (FSH) secretion, and continuously produced gonadotropin-releasing hormone (GnRH), which all contribute to elevated androgen secretions, ovulatory failure, and insulin resistance (Yalan and Jie, 2022).

An imbalance between antioxidants and oxidants and the production of too many reactive oxygen species (ROS) is called oxidative stress (Kıran et al., 2023). Patients with PCOS have higher-than-normal markers in oxidative circulation, suggesting a role for oxidative stress in the pathophysiology of PCOS (Sulaiman et al., 2018). Insulin resistance has been associated with oxidative stress and the generation of reactive oxygen species. Oxidative stress decreases insulin production from the pancreatic β cells and hinders glucose absorption in muscle and adipose tissue (Almulathanon et al., 2021). Additionally, hyperinsulinemia hinders nitric oxide (NO) secretion from vascular endothelium in PCOS patients (Hassani et al.,2012). Consequently, there is a drop in the membrane fluid, which raises intracellular calcium levels and causes endothelial dysfunction—an early sign of atherosclerosis that may manifest, also an increase in

ROS production in PCOS (Dalal et al., 2020). Malondialdehyde (MDA) is a significant end product that is frequently employed as a biomarker to evaluate oxidant status since it corresponds with the level of lipid peroxidation (Rudnicka et al., 2022). Insulin resistance, hyperandrogenism, dyslipidemia, and obesity associated with PCOS likely raise MDA levels while lowering those of antioxidant enzymes (Fathi, 2020).

Adropin is a secreted protein encoded by the energy homeostasis-associated gene (ENHO) (Jasaszwili et al., 2020). The relationship between adropin and metabolic diseases has been confirmed. Numerous tissues and organs, including the pancreas, liver, brain, kidneys, and myocardium, have been found to contain Adropin (Ali et al., 2022). It protects against cardiovascular disease development by regulating lipid metabolism, lowering insulin resistance, and enhancing the function of vascular endothelial cells. It has anti-inflammatory properties as well (Sato et al., 2018). It was demonstrated in the Aydın et al. study that Adropin level is a prognostic signal (Aydin et al., 2013).

This study evaluated and compared the relationship of Adropin with oxidative stress as a clinical predictor for the development of polycystic ovarian syndrome.

MATERIALS AND METHODS

Study group

This case-control study included (110) individuals with an age range from 15 to 45 years. Participants were selected from the Al-Batoul Teaching Hospital (Obstetrics and Gynecology) in Mosul City, Iraq from January 2023 to the end of April 2023. Informed consent was taken from each participant. Approved by Nineveh Health, the Iraqi Ministry of Health the study. Participants were divided into two Group 1: a non-PCOS (apparently healthy) group consisting of 47 women with regular menstrual cycles.
Group 2 included a PCOS consisting of 63 women, PCOS was diagnosed based on Rotterdam criteria (Rotterdam, 2013) including women present with Oligomenorrhea (irregular menstrual periods), Hyperandrogenism, and Polycystic ovaries (on the ultrasound). information was recorded according to the questionnaire paper.

Exclusion Criteria

Women who suffered from breast cancer, endometriosis, and uterine fibroids. Patients on estrogen replacement therapy, Women with diabetes, mental disorders, hyper- and hypothyroidism were also removed.

Clinical and Demographic Examination

All Participants underwent a thorough physical test with their weight, height, waist, and blood pressure being recorded. Body mass index (BMI) was calculated as the weight (kg) to height squared (m^2) ratio (Ross et al., 2020). Waist-to-height ratio (WHtR) was calculated as the ratio of waist circumference (cm) to height (cm) (Yoo, 2016) .

Blood assay

Venous blood was taken from all participants into gel tubes between 9:00 a.m. and 10:00 a.m. following 12 h of fasting for Clinical parameters and centrifuged at 3500 rpm for 10 min and the serum was separated.

Adropin and Insulin were measured by using an Enzyme-Linked Immunosorbent Assay (ELISA) kit from SUN LONG Biological Technology Co., Ltd kit (China).

Serum glucose and lipid profile including triglycerides (TG), total cholesterol (TC), and high-density lipoprotein (HDL-C), were estimated using a ready-made assay (kits) from the company (BIOLABS) and using enzymatic methods.

Non-high-density lipoprotein (Non-HDL) = TC–HDL (Calling et al., 2021) the homeostasis model assessment [HOMA-IR=insulin (μIU/ mL) × glucose (mg/dL)/405] was used to estimate insulin resistance (IR) (Jasim et al., 2021).

Estimation of the activity of arylesterase (Allwsh and Jasim, 2008), peroxidase (Nelson and Kulkarni, 1990), the concentration of malondialdehyde (MDA) (Sabah and Allwsh, 2020), glutathione (GSH), vitamin C and vitamin E (Almulathanon et al., 2021), and peroxynitrite (Thikra and Noori, 2023) in serum.

Data Analysis

The data is shown as mean ± SE. The comparison between the PCOS group and the control group non-PCOS 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

The Clinical and Demographic Features

Table 1 summarizes the clinical and demographic features of all the women involved in this study. There was a significant increase ($P \leq 0.05$) observed in the BMI, waist circumference, WHtR, systolic blood pressure (SBP), and diastolic blood pressure (DBP) in patients with PCOS compared to the healthy control group non-PCOS, however, the patients' ages for (POS) were lower than those of the control females, as well as a significant increase ($P \leq 0.05$) in TC, TG, non-HDL, glucose, insulin,

Table 1. The Clinical and Demographic Features of PCOS

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*
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*
TC (mg\dl)	148.7±27	190.3± 21*
TG (mg\dl)	85.7±15.2	116.3±16.4*
HDL (mg\dl)	48.16±5.1	34.08±2.9 *
Non -HDL (mg\dl)	96.1±18	156.2±21.9 *

* Significant at the level (P ≤ 0.05)

Table 2. The level of Adropin for PCOS

Age (year)	Adropin (ng\ml)	
	non-PCOS (Mean ± SD)	PCOS (Mean ± SD)
14-25	0.68 ± 0.18 a	0.41 ± 0.19 * a
26-45	0.39 ± 0.16 b	0.24 ± 0.11 * b
Total	0.53 ± 0.12	0.32 ± 0.14 *

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)

and insulin resistance (HOMA-IR) but a significant decrease in HDL in PCOS as compared to a non-PCOS group.

The levels of Adropin and Oxidative Stress Factors for PCOS

Table 2. indicates that there is a significant decrease in the level of Adropin in the serum of PCOS patients and the non-PCOS group (P≤0.05) getting older. Also, a significant decrease in the level of Adropin in PCOS patients compared to its level in the non-PCOS group (P≤0.05).

Moreover, a significant increase (P ≤ 0.05) in the activity of peroxidase, concentration of peroxynitrite, and malondialdehyde in PCOS patients than in non-PCOS. Also, the concentration of vitamin C, vitamin E, glutathione, and the activity of the arylesterase was significantly lower (P ≤ 0.05) in PCOS patients than in non-PCOS as shown in Table 3.

Correlation between Adropin and clinical parameters for PCOS

Table 4 shows a negative correlation (p≤0.05) between Adropin levels and BMI, blood pressure (SBP / DBP), TC, TG, non-HDL, glucose, insulin, (HOMA-IR), and Malondialdehyde. In addition, a positive correlation between Adropin and HDL in PCOS.

Table 3. Oxidative Stress Factors for PCOS

Oxidative Stress Factors	non-PCOS (Mean ± SD)	PCOS (Mean ± SD)
Glutathione (µmol/l)	2. 9 ± 0.6	**1. 3 ± 0. 3***
vitamin C (mg\dl)	3. 5±0.6	**2. 6±0.4** *
vitamin E (µmol/l)	33. 8 ± 4.7	**19.5 ± 3.**8 *
peroxynitrite(µmol/l)	18.1 ± 3.5	**39.9 ± 11.1***
Aryleasterase (U/ml)	90.3 ± 17	13***±**78
Malondialdehyde (µ mol/l)	8 ± 0.00.19	**0.33 ± 0.1***
Peroxidase (U/ml)	67.7 ± 14.5	**110.2 ± 15.1 ***

*significant at the level (P ≤ 0.05)

Table 4. Correlation between Adropin and clinical parameters for PCOS

Adropin	
Parameters	**PCOS (R-value)**
SBP / DBP (mm Hg)	-0.835*
BMI-Kg\m²	-0.842*
F.B.S(mg\dl)	-0.5 02*
Insulin(µIU\ml)	-0.518 *
HOMA-IR	-0.4 14*
TC (mg\dl)	-0.521*
TG (mg\dl)	-0.504*
HDL	0.497*
Non-HDL	0.464
Glutathione (µmol/l)	0.611
vitamin C (mg\dl)	0.753
vitamin E (µmol/l)	0.542
peroxynitrite(µmol/l)	0.509
Aryleasterase (U/ml)	0. 527*
Malondialdehyde (µ mol/l)	0.304*
Peroxidase (U/ml)	0.869

*Significant at the level (P ≤ 0.05)

DISCUSSION

PCOS's pathophysiology is still complicated although insulin resistance, abdominal obesity, and androgen excess can all contribute to PCOS. Furthermore, oxidative stress plays a significant part in PCOS (Turan et al., 2015). Abnormalities in the metabolic process have been linked to PCOS because the mitochondria may be the primary organ responsible for the weak metabolism of energy (Cozzolino and Seli, 2020), as well as, the increased blood pressure, obesity, lipid, glucose, insulin, and (HOMA-IR), which can induce oxidative stress by promoting preadipocyte proliferation (Abdallha and Allwsh, 2023) and also, in PCOS patients, oxidative stress is linked to persistent anovulation, hyperandrogenism, insulin resistance, and inflammation. moreover, it impairs female fertility and is linked to several pregnancy problems, miscarriage, and anovulation (Blair et al., 2013).

The low level of Adropin is due to an increase in risk factors associated with polycystic ovary syndrome, as 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), and an increase in Adropin was found for (PCOS) after adjusting the level of (SHBG) (Artemis et al., 2018), a drop in Adropin is also associated with the development of insulin resistance, which has a role in the syndrome (Gao et al., 2015). In addition, it found that a decrease in Adropin was more evident in obese women with (PCOS), as a decrease was associated with a higher body mass index value in (PCOS) indicating that it 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 (Kuliczkowska et al., 2019; Soltani et al., 2023).

The state of oxidative stress is associated with the pathophysiology of polycystic ovary syndrome, especially in patients with overweight or abdominal obesity (Robert et

al., 2016) and the reason for the high concentration of malondialdehyde resulting from lipid peroxides is due to the high Reactive Oxygen Species (ROS) generated from Oxidative stress, high blood sugar, and insulin resistance in patients with PCOS (Oyebanji, and Asaolu, 2020) , as well as, the increase in androgen in women with PCOS also stimulates an increase in the formation of ROS and thus leads to the depletion of glutathione (Sulaiman et al., 2018), and the reason for the decreased activity of the aryl ester enzyme may be due to its association with HDL (Allwsh and Jasim, 2008) which decreased in PCOS, addition the use of metformin treatment stimulates the activity of the aryl esterase enzyme (Carlioglu et al., 2014). Vitamin E protects polyunsaturated fatty acids from peroxidation reactions, vitamin C also works to reduce oxidants, and antioxidant vitamins work to maintain the balance of oxidants and antioxidants (Oyebanji, and Asaolu, 2020).

The relationships between Adropinandglucose, 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 (Gao et al., 2015).

CONCLUSIONS

This study demonstrated that significantly lower serum levels of Adropin in PCOS with the oxidative/antioxidative balance being changed in favor of oxidative status. so, serum Adropin levels may have a significant role in the initiation and development of PCOS.

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Ethical statements for human/animal experiments

The study was approved by the institutional ethics committee "University of Mosul" and the Iraqi Ministry of Health - Nineveh Health. The study approval number and date on (8 /1/2023) (Research No. 2023015). informed consent was obtained in writing by each participant. Each participant was informed about the study follow-up before enrolling for the study.

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Conflicts of Interest: The authors declared no conflicts of interest

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