Journal of Research in Medical and Dental Science
2022, Volume 10, Issue 5, Page No: 13-17

Available Online at: www.jrmds.in
eISSN No. 2347-2367: pISSN No. 2347-2545

Assessment the Levels of Leptin, Adiponectin, and Insulin Resistance in Iraqi Women with Polycystic Ovary Syndrome (PCOS)

Afrah N Faris[1*], Khalid G Al-Fartosi[1], Wassan R Al-Khafaji[2]

[1]Department of Biology, College of Science, University of Thi-Qar, Iraq
[2]Department of Obstetrics and Gynecology, College of Medicine, University of Thi-Qar, Iraq

ABSTRACT

The objectives of this paper is to investigate the leptin and adiponectin levels in women with polycystic ovary syndrome (PCOS)., as well as their relationship to insulin resistance. A case-control study was conducted in private health institutions in Thi-Qar Governorate, iraq from March 1, 2021 to September 30, 2021, and included 100 married women with PCOS and infertility and 80 healthy married couples, who diagnosed by gynecologists. Venous blood was sampled from fasting participants for the determination of parameters of this study. The results showed a significant elevation in the levels of BMI, leptin, fasting blood sugar(FBS), insulin and HOMA-IR while there was a significant decline in the level of adeponectin in the patients with PCOS group compared to the control group regardless of body mass index ($p<0.05$). According to the study's findings, leptin and adiponectin levels might be considered useful indicators in the early diagnosis of PCOS, as well as treatment targets, it appears to be a positive relationship between insulin resistance and leptin and a negative relationship with adiponectin in PCOS patients.

Key words: Leptin, Adeponectin, Insulin resistance, PCOS

HOW TO CITE THIS ARTICLE: Afrah N Faris, Khalid G Al-Fartosi, Wassan R Al-Khafaji, Assessment the Levels of Leptin, Adiponectin, and Insulin Resistance in Iraqi Women with Polycystic Ovary Syndrome (PCOS), J Res Med Dent Sci, 2022, 10 (5):13-17.

Corresponding author: Afrah N Faris

e-mail✉**:** mutazalharbi84@gmail.com

Received: 04-April-2022, Manuscript No. JRMDS-22-57336;

Editor assigned: 06-April-2022, **PreQC No.** JRMDS-22-57336 (PQ);

Reviewed: 20-April-2022, QC No. JRMDS-22-57336;

Revised: 25-April-2022, Manuscript No. JRMDS-22-57336 (R);

Published: 02-May-2022

INTRODUCTION

PCOS, or polycystic ovary syndrome, is a widely known endocrine disorder in women distinguished by hyperandrogenism during reproductive age [1]. Women with PCOS often have menstrual problems and infertility issues. Moreover, it may contribute to long-term health problems like diabetes and heart disease, cancer of the uterus and mood disorders [2.] The exact causes of PCOS are very complex and still not clear. There are many suggested etiologies for PCOS. But it is not fully supported, in general, this hormonal imbalance consists of a combination of excess androgen and insulin resistance. In addition to environmental and genetic factors that contribute to this hormonal imbalance, all of these causes the development of PCOS [3]. Symptoms and signs vary among women with PCOS, it includes a combination of hyperandrogenism (hirsutism, alopecia, acne, high blood testosterone), obesity and severe menstrual irregularity (oligomenorrhea or amenorrhea) [4]. Adipose tissue is a major source of energy for the human body. It is also secreting adipocytokines adiponectin and leptin [5]. Leptin is a hormone that regulates body weight, discovered in 1991, 167 amino acids, secreted by adipose tissue and hypothalamus, stomach, placenta, skeletal muscle, and mammary epithelial cells [6,7]. Polycystic ovary syndrome is associated with metabolic disorders such as obesity and resistance Insulin [8], as obesity occurs in about half of women with polycystic ovary syndrome 70% of patients with – cysts [9], while there is insulin resistance in about 50 Independently of obesity [10]. Given the well-known link between leptin and PCOS obesity and insulin action, it is possible to hypothesize that leptin plays a role in its pathogenesis of PCOS [11]. Adiponectin (a protein with 244 amino acids and a molecular weight of 28 kDa) is secreted by adipose tissues that has anti-inflammatory properties and can positively modulate the endocrine system by increasing insulin sensitivity in obese animals and humans [12,13]. Adiponectin might be responsible for the metabolic and neuroendocrine (hormonal) issues that are associated with obesity and obesity-related diseases, such as polycystic ovary syndrome [14]. The purpose of this study was to focus on leptin and adiponectin levels in women with PCOS, as well as their relationship to insulin resistance.

SUBJECTS AND METHODS

Subjects

This is a case control study that lasted from 1 March

2021 to 30 September 2021 and included 100 married infertile PCOS patients and 80 married healthy controls from private health institutions in Thi-Qar governorate, Iraq. The following two groups were investigated: 1-patients, infertile women with PCOS, their age ranged from (18 – 41) years. All of them were diagnosed and selected by gynecologists using the Rotterdam criteria [15]. This study excluded PCOS patients with the following criteria: thyroid problems, acanthosis nigricans, hyperprolactinemia, Cushing's disease, Congenital adrenal hyperplasia with late onset, using oral contraceptives and ovulation stimulants. 2-The control group, 80 healthy women, have matching age to patients, there were normovulatory women.

Methods

All study participants underwent clinical evaluation and anthropometrics (weight, Height). Venous blood was sampled from fasting participants in luteal phase for determination of parameters in this study. Elisa technology used to assay the levels of leptin (by kit of Mediagnost, Germany), adeponectin (by kits of sunlong, Chine) Also Enzymatic colorimetric test used to assay the level of fasting blood sugar (FBS) by Cobas integra 400 plus (Kits and instrument Roche- Germany) and insulin level were determined by using Cobas 411 immunoassay analysis (Kits and instrument Roche-Germany). Subgroups: control and patients groups were classified into two groups based on the BMI value, the first group being normal weight (BMI<24) and the second group being overweight and obese (BMI>24) [16].

insulin resistance (HOMA-IR) was calculated as: glucose (mg/dL) × insulin (μU/mL)/405.

Statistical analysis

All results are shown as the mean ± standard deviation (SE). Individual hormone levels were examined to see whether there were any variations in mean levels. using the student t-test.

RESULTS

Study's parameters in general for patients and control groups

Table 1 explain a significant elevation in the levels of BMI, leptin, FBS, insulin and HOMA-IR while there was a significant decline in the level of adeponectin in the patients with PCOS group compared to the control group ($p<0.05$).

Levels of leptin, adeponectin and insulin resistance according BMI categories

The results of this study also recorded a significant increase in the level of leptin in the first and second BMI group of patients compared to the first and second BMI group of the control group respectively. There was non-significant difference in the level of leptin in two BMI groups for each control and patients' groups ($p<0.05$) as shown in Table 2.

Adeponectin

Table 3 explain a significant decline in the levels of adeponectin in the first and second BMI group of patients compared to matching BMI group of the control group. There was non-significant difference in the level of adeponectin in two BMI groups for each control and patients' groups ($p<0.05$).

HOMA-IR

The results of the current study also showed a significant increase in HOMA-IR in the first and second BMI group of patients compared to the first and second BMI group of the control group respectively. There was non-significant difference in HOMA-IR in two BMI groups for each control and patients' groups ($p<0.05$) as shown in Table 4.

Table 1: BMI, leptin, adeponectin and insulin resistance (with related factors) of the control and patients with PCOS groups.

Parameters	Control No. 80	Patients No. 100	t. test p. value
	Mean ± SD		
BMI	24.3 ± 0.95	30.03 ± 4.59	<0.001
Leptin (ng/ml)	20.2 ± 3.08	27.1 ± 7.09	<0.001
Adeponectin (ng/ml)	3.37 ± 0.72	2.31 ± 0.65	<0.001
FBS (mg/dl)	94.0 ± 7.58	120.9 ± 9.95	<0.001
Insulin (μU/mL)	4.31 ± 0.96	25.7 ± 5.43	<0.001
HOMA-IR	1.01 ± 0.25	7.68 ± 1.70	<0.001

Table 2: Leptin levels in control and patients' groups According to BMI categories.

Leptin (ng/ml)	Cases No.	Control Mean ± SD	Cases No.	Patient Mean ± SD	t. test p. value
Normal BMI	30	19.6 ± 3.24	14	29.8 ± 6.95	<0.001
Overweight & Obesity	50	20.6 ± 2.85	86	26.7 ± 7.08	<0.001
P. value	80	0.183	100	0.123	

Table 3: Adeponectin levels in control and patients' groups according to BMI categories.

ADP (ng/ml)	Cases No.	Control Mean ± SD	Cases No.	Patient Mean ± SD	t. test p. value
Normal BMI	30	3.34 ± 0.70	14	2.50 ± 0.71	<0.001
Over weight & Obesity	50	3.38 ± 0.74	86	2.29 ± 0.63	<0.001
P. value	80	0.89	100	0.27	

Table 4: HOMA-IR levels in control and patients' groups According to BMI categories.

HOMA-IR	Cases No.	Control Mean ± SD	Cases No.	Patient Mean ± SD	t. test p. value
Normal BMI	30	0.95 ± 0.24	14	8.03 ± 2.34	<0.001
Over & Obesity	50	1.03 ± 0.26	86	7.62 ± 1.58	<0.001
P. value	80	0.187	100	0.4	

DISCUSSION

The current study focuses on the role of adipose tissue hormones in PCOS, also taking the body's metabolic condition into account. Adipokines with potential effects on reproductive function are secreted by white adipose tissue. Leptin and adiponectin are the two most researched adipokines in this issue; their effects on fertility have been attributed to either central effects on the hypothalamus or peripheral effects on the ovary, reproductive tract, endometrial development, or embryo implantation [17].

Obese and non-obese women with PCOS had low adiponectin levels and high leptin levels [18,19]. This is consistent with the results of our study. Also, the results of this study showed a significant increase in insulin resistance in PCOS patients, and these results are consistent with other study which showed that polycystic ovary syndrome is associated with metabolic disorders such as obesity and Insulin resistance [8]. Leptin functions as a metabolic regulator of reproductive capability by informing GnRH neurons about the amount of energy stored in the body [20]. It is suggested that increased leptin levels are linked to the risk of insulin resistance, metabolic problems, infertility, and cardiovascular disease in PCOS, and may even contribute to the development of PCOS [21]. It has been demonstrated that leptin secretion is related to sex hormones [21]. High leptin levels also have a role in the pathogenesis of PCOS by enhancing GnRH release, activating pituitary gonadotrophs, or stimulating the ovaries [22]. Intraneuronal pathways including neuropeptide-Y, proopiomelanocortin, and kisspeptin modulate leptin's effects on GnRH [23].

Leptin resistance is a common feature in obese people, and it has been linked to ovulatory failure and infertility (frequently associated with PCOS) [24]. Hyperleptinemia can directly impair mature oocyte development as well as ovarian and adrenal steroidogenesis [25].

At a physiological level, leptin has been shown to increase oocyte maturation via activating the STAT signal transduction system [26]. High amounts of circulating leptin inhibited folliculogenesis in mice, but low levels of circulating leptin aided the transition from primary to secondary follicle [27]. Leptin may have a role in preovulatory follicular development, oocyte fertilization ability, and eventual embryo implantation potential [28]. Leptin hormone Ineffective in PCOS, we suggest, this due to a rise in leptin hormone levels to the stage of leptin resistance, which is causally due to high insulin and the state of insulin resistance in PCOS patients. Obese and non-obese women, since leptin is affected by the volume and distribution of body fat rather than body mass, as previously stated. The adipokines are the link between PCOS, obesity, and insulin resistance [29,30]. Adiponectin levels are decreased in both PCOS and prediabetic individuals. Li et al. [31] underlined that adiponectin levels were reduced in women with PCOS, which linked with PCOS independent of weight or insulin resistance.

Adiponectin activates fatty acid oxidation and glucose absorption in vitro [32]. Thiazolidinediones' pharmacological impact on insulin sensitivity entails a rise in both total and HMW adiponectin [33]. Adiponectin lowers tissue triglyceride levels while increasing insulin signaling [34]. Adiponectin inhibits gluconeogenesis in the liver, which may explain for its acute glucose-lowering effects [35]. Insulin lowers adiponectin levels [36], and adiponectin levels are higher in type 1 diabetics than in healthy controls [37]. Hyperinsulinemia may reduce circulating adiponectin levels, resulting in insulin resistance [38]. Adiponectin has been shown to inhibit LH and GnRH release [39], implying a function in the control of the hypothalamo-pituitary-gonadal axis [40]. Obese people had lower circulating Adiponectin levels, which are inversely connected to testosterone levels [41]. Testosterone has an inhibitory impact on adipocytes' production of HMW Adiponectin [42]. Women with PCOS have a decrease in HMW Adiponectin that is independent of BMI and insulin receptor (IR) [43]. It influences ovulation and steroidogenesis in a pleiotropic manner [44]. However, we considered in this study that the high level of leptin in PCOS patients had progressed to the stage of leptin resistance, especially given the ongoing increase in body mass index and the lack of weight reduction, which is one of the most significant roles of the hormone leptin. Furthermore, as with obesity, leptin resistance in pregnancy may be caused by impaired transport across the blood–brain barrier or by the sequestration of bioactive leptin in the circulation by a soluble receptor [45]. Frisch hypothesized in 1974 that the capacity to reproduce required a minimum level of body fat to serve as the minimal reserve of energy required for ovulation, menstruation, and intended pregnancy [46]. Body mass index had no effect on the outcomes of this study since the parameter's decline or elevation was constant in obese and non-obese women. To explain this case, we propose that PCOS occurs in response to a metabolic disorder that occurs when the fat mass in a woman's body reaches a certain threshold, particularly around the organs in the abdominal area, serving as the minimal fat amount to cause a metabolic disorder so that the body reaches the stage of insulin resistance and leptin resistance (taking into account other non-metabolic disorders that cause insulin resistance and leptin resistance such as genetics, environment and food) which lead to onset of PCOS, and

the issue develops with an increase in body mass index.

CONCLUSION

According to the results of this study, the levels of leptin and adiponectin can be considered effective biomarkers in the early diagnosis of PCOS, especially in non-obese women, and can be used to predict the risk of developing PCOS in women without obvious symptoms, With the possibility of considering these indicators as therapeutic targets for PCOS. it appears to be a positive relationship between insulin resistance and leptin and a negative relationship with adiponectin in PCOS patients. It was also showed that parameters abnormalities in this study are not related to BMI in PCOS, while BMI enhances PCOS complications.

REFERENCES

1. Azziz R. New insights into the genetics of polycystic ovary syndrome. Nature Rev Endocrinol 2016; 12:74-75.
2. Thomson RL, Buckley JD, Brinkworth GD. Exercise for the treatment and management of overweight women with polycystic ovary syndrome: a review of the literature. Obesity Rev 2011; 12:202-210.
3. Garad R, Teede H, Moran L. An evidence-based guideline for polycystic ovary syndrome. Australian Nurs J 2011; 19:30.
4. Mohd M, Maqbool M, Dar MA, et al. Polycystic ovary syndrome, a modern epidemic: An overview. J Drug Delivery Therapeu 2019; 9:641-644.
5. Gale SM, Castracane VD, Mantzoros CS. Energy homeostasis, obesity and eating disorders: Recent advances in endocrinology. J Nutr 2004; 134:295-298.
6. Whipple T, Sharkey N, Demers L, et al. Leptin and the skeleton. Clin Endocrinol 2002; 57:701-711.
7. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metabol 2004; 89:2548-2556.
8. Goodarzi MO, Dumesic DA, Chazenbalk G, et al. Polycystic ovary syndrome: Etiology, pathogenesis and diagnosis. Nat Rev Endocrinol 2011; 7:219-231.
9. Rojas J, Chávez M, Olivar L, et al. Polycystic ovary syndrome, insulin resistance, and obesity: Navigating the pathophysiologic labyrinth. Int J Reproductive Med 2014; 1-17.
10. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol 2014; 6:1-13.
11. Chakrabarti J. Serum leptin level in women with polycystic ovary syndrome: correlation with adiposity, insulin, and circulating testosterone. Annals Med Health Sci Res 2013; 3:191-196.
12. Kim DH, Vanella L, Inoue K, et al. Epoxyeicosatrienoic acid agonist regulates human mesenchymal stem cell–derived adipocytes through activation of HO-1-pAKT signaling and a decrease in PPARγ. Stem Cell Develop 2010; 19:1863-1873.
13. Zhao L, Fu Z, Liu Z. Adiponectin and insulin cross talk: the microvascular connection. Trends Cardiovas Med 2014; 24:319-324.
14. Arita Y, Kihara S, Ouchi N, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Communication 1999; 257:79-83.
15. ESHRE TR, ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertility Sterility 2004; 81:19-25.
16. Bu Z, Dai W, Guo Y, et al. Overweight and obesity adversely affect outcomes of assisted reproductive technologies in polycystic ovary syndrome patients. Int J Clin Exp Med 2013; 6:991.
17. Dos Santos E, Duval F, Vialard F, et al. The roles of leptin and adiponectin at the fetal-maternal interface in humans. Hormone Mol Biol Clin Invest 2015; 24:47-63.
18. Toulis KA, Goulis DG, Farmakiotis D, et al. Adiponectin levels in women with polycystic ovary syndrome: A systematic review and a meta-analysis. Human Reprod Update 2009; 15:297-307.
19. Chou SH, Mantzoros C. Role of leptin in human reproductive disorders. J Endocrinol 2014; 223:49-62.
20. Watanobe H. Leptin directly acts within the hypothalamus to stimulate gonadotropin-releasing hormone secretion *in vivo* in rats. J Physiol 2002; 545:255-268.
21. Zheng SH, Du DF, Li XL. Leptin levels in women with polycystic ovary syndrome: A systematic review and a meta-analysis. Reproduc Sci 2017; 24:656-670.
22. Quennell JH, Mulligan AC, Tups A, et al. Leptin indirectly regulates gonadotropin-releasing hormone neuronal function. Endocrinol 2009; 150:2805-2812.
23. Hausman GJ, Barb CR, Lents CA. Leptin and reproductive function. Biochem 2012; 94:2075-2081.
24. Rich-Edwards JW, Goldman MB, Willett WC, et al. Adolescent body mass index and infertility caused by ovulatory disorder. Am J Obstetr Gynecol 1994; 171:171-177.
25. Blüher S. Mantzoros CS. Leptin in reproduction. Current Opinion Endocrinol Diabetes Obes 2007; 14:458–464.
26. Matsuoka T, Tahara M, Yokoi T, et al. Tyrosine phosphorylation of STAT3 by leptin through leptin receptor in mouse metaphase 2 stage oocyte. Biochem Biophy Res Communic 1999; 256:480-484.
27. Panwar S, Herrid M, Kauter KG, et al. Effect of passive immunization against leptin on ovarian follicular development in prepubertal mice. J Reproduc Immunol 2012; 96:19-24.
28. Li MG, Ding GL, Chen XJ, et al. Association of serum and follicular fluid leptin concentrations with granulosa cell phosphorylated signal transducer and activator of transcription 3 expression in fertile patients with polycystic ovarian syndrome. J Clin Endocrinol Metabol 2007; 92:4771-4776.
29. Dunaif A, Thomas A. Current concepts in the polycystic

ovary syndrome. Ann Rev Med 2001; 52:401-419.

30. Andersen M, Glintborg D. Diagnosis and follow-up of type 2 diabetes in women with PCOS: a role for OGTT?. Eur J Endocrinol 2018; 179:1-14.
31. Li H, Chen Y, Li Y, et al. A case-control study of correlation between serum adiponectin levels and polycystic ovary syndrome. Zhonghua Chan 2015; 50:814-818.
32. Fasshauer M, Klein J, Kralisch S, et al. Growth hormone is a positive regulator of adiponectin receptor 2 in 3T3-L1 adipocytes. FEBS letters 2004; 558:27-32.
33. Wang Y, Xu A, Knight C, et al. Hydroxylation and glycosylation of the four conserved lysine residues in the collagenous domain of adiponectin: potential role in the modulation of its insulin-sensitizing activity. J Biol Chem 2002; 277:19521-19529.
34. Yamauchi T, Kamon J, Waki H, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nature Med 2001; 7:941-946.
35. Yamauchi T, Kamon J, Minokoshi YA, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nature Med 2002; 8:1288-1295.
36. Motoshima H, Wu X, Sinha MK, et al. Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. J Clin Endocrinol Metabol 2002; 87:5662-5667.
37. Imagawa A, Funahashi T, Nakamura T, et al. Elevated serum concentration of adipose-derived factor, adiponectin, in patients with type 1 diabetes. Diabetes Care 2002; 25:1665-1666.
38. Yadav A, Kataria MA, Saini V, et al. Role of leptin and adiponectin in insulin resistance. Clinica Chem Act 2013; 417:80-84.
39. Wen JP, Lv WS, Yang J, et al. Globular adiponectin inhibits GnRH secretion from GT1-7 hypothalamic GnRH neurons by induction of hyperpolarization of membrane potential. Biochem Biophy Res Commun 2008; 371:756-761.
40. Psilopanagioti A, Papadaki H, Kranioti EF, et al. Expression of adiponectin and adiponectin receptors in human pituitary gland and brain. Neuroendocrinol 2009; 89:38-47.
41. Escobar-Morreale HF, Insenser M, Cortón M, et al. Proteomics and genomics: A hypothesis-free approach to the study of the role of visceral adiposity in the pathogenesis of the polycystic ovary syndrome. Proteomics Clin Appl 2008; 2:444-455.
42. Xu A, Chan KW, Hoo RL, et al. Testosterone selectively reduces the high molecular weight form of adiponectin by inhibiting its secretion from adipocytes. J Biol Chem 2005; 280:18073-18080.
43. O'Connor A, Phelan N, Tun TK, et al. High-molecular-weight adiponectin is selectively reduced in women with polycystic ovary syndrome independent of body mass index and severity of insulin resistance. J Clin Endocrinol Metabol 2010; 95:1378-1385.
44. Michalakis, KG, Segars JH. The role of adiponectin in reproduction: From polycystic ovary syndrome to assisted reproduction. Fertil Steril 2010; 94:1949-1957.
45. Henson MC, Castracane VD. Leptin in pregnancy: An update. Biol Reproduc 2006; 74:218-229.
46. Frisch RE, McArthur JW. Menstrual cycles: Fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science 1974; 185:949-951.