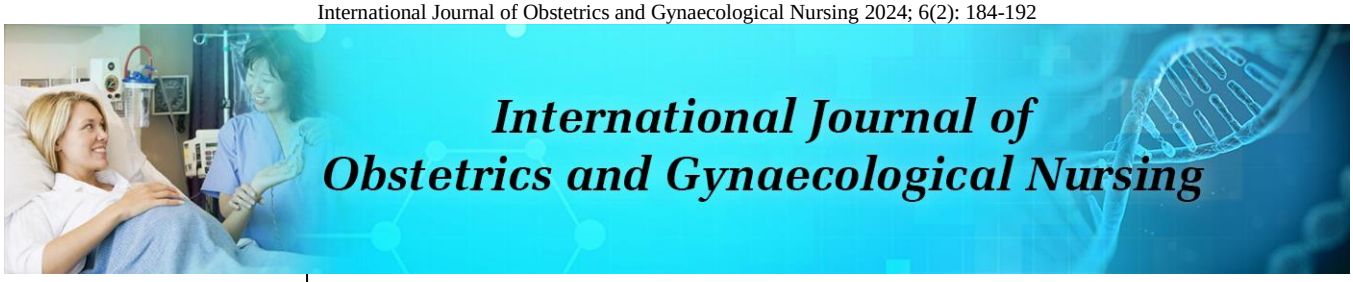

E-ISSN: 2664-2301
P-ISSN: 2664-2298
www.gynaecologicalnursing.com
IJOGN 2024; 6(2): 184-192
Received: 16-11-2024
Accepted: 27-12-2024

Rana Hasan Ahmed
Gynecology and ObstetricsBoard, Tikit Teaching Hospital, Iraq

Corresponding Author:
Rana Hasan Ahmed
Gynecology and ObstetricsBoard, Tikit Teaching Hospital, Iraq

Adipocytokines as a fertility factor: A connection between obesity and PCOS (Polycystic Ovary Syndrome)

Rana Hasan Ahmed

DOI: https://doi.org/10.33545/26642298.2024.v6.i2c.175

Abstract
Background: Obesity is a pandemic that is still growing and is linked to metabolic, androgenic, and reproductive comorbidities in women. A complex endocrinopathy, polycystic ovarian syndrome (PCOS) is characterized by hyperandrogenic, reproductive, and metabolic dysfunctional characteristics. PCOS and obesity frequently coexist. The metabolic syndrome that is linked to PCOS and its clinicopathological symptoms are mostly caused by insulin resistance and the hyperinsulinemia that follows.
Objective: This study's main goal was to assess the amounts of the proteins leptin, resistin, retinol binding protein-4, and chemerin in people with PCOS.
Methods: The study was conducted from March 1st, 2024, to June 30th, 2024, at Tikit Teaching Hospital. There were 150 female patients in the trial, ranging in age from 15 to 45. following the completion of clinical and medical examinations by a physician who specializes in this area. In addition to selecting a random group, 75 samples of healthy females in the same age range as the control group were included.
Results: The ill groups had considerably greater blood concentrations of Leptin, Resistin, Retinol binding protein-4, and Chemerin (p<0.01) compared to the healthy individuals (C).
Conclusion: Obesity is far more common in PCOS patients, and it is a significant and separate cause of PCOS. Because adipokines allow adipose tissue to communicate with the brain, ovaries, and uterus, this tissue is concerned with the regulation of the law in the metabolic homes of women who have PCOS. According to the data above, adipokines are most likely implicated in the development of PCOS.

Keywords: Polycystic ovary syndrome, diabetes, liptin, resistin, retinol binding protein-4, chemerin, women

Introduction
Among the most renowned Polycystic ovarian syndrome (PCOS) is an endocrine system condition that affects women. 5-10% of women in the reproductive age range have PCOS, which is one of the common reasons of female infertility. As a wandering illness, its symptoms include anovulation, polycystic ovaries, overindulgence, hirsutism, acne, and infertility [1]. Metabolic problems like obesity, dyslipidemia, hyperinsulinemia, and insulin resistance are very common in PCOS patients. Furthermore, it has recently been shown that individuals with PCOS have changed metabolic characteristics, including misaligned amino acids, delayed tricarboxylic acid cycle, and enhanced glycolysis [2]. Consequently, those with PCOS may be somewhat more likely to develop type 2 diabetes and cardiovascular disease (CVD) [3]. The majority of PCOS sufferers are overweight. Overweight, obesity, or concentrated obesity are more common in women with PCOS. On the other hand, obesity is a global health concern today. It is characterized as an excess of fat buildup in the body, or more accurately, a lack of dietary regulation over the typical intake of fat from food. An increase in adipocyte volume and quantity is one of its defining characteristics. The World Health Organization defines overweight as having a body mass index of 30 or more. There are instances in which obesity has negative health effects. Obesity is well recognized to be associated with a number of disorders, including metabolic syndrome, type 2 diabetes, and cardiovascular disease. Numerous scholars have investigated the impact of obesity on a woman's ability to conceive.

Pregnancy potential appeared to be decreased in overweight women. The time it takes for implantation is shortened in obese women; they also lead to irregular menstrual cycles, increase the risk of miscarriages, and significantly delay ovulation, which lowers the likelihood of conception. However, body fat distribution is very important since obesity that is concentrated in the midsection and abdomen is linked to insulin resistance and has a greater effect on reproduction. The central distribution of body fat is higher in PCOS-affected women and is associated with both and rogenism and IR.

People that are obese have much higher amounts of fat mass, which is because fat stores a lot of energy. It has now been determined that adipose tissue serves as both a significant endocrine structure and a vast energy storage. Adipose tissue has been shown to have a significant role in regulating several physiological processes, including as the immune system, reproduction, and the metabolism of glucose and lipids, by secreting a series of bioactive cytokines known as adipokines. Adipokines include of specific adipokines such as leptin, resistin, APN, visfatin, and omentin, as well as non-specific cytokines such as RBP4, LCN2, chemokines, interleukin 6 (IL6), IL1b, and TNFa [6]. An abnormally high concentration of adipokines has been linked to both IR and T2DM. Adipose tissue dysfunction in PCOS patients is thought to be caused by increased production of proinflammatory adipokines such as TNFa and decreased production of "good" adipokines such as APN. There is abundant evidence that obesity has a role in the development of PCOS. In this study, we looked at the roles that many identified adipokines both well-known and unique to fats have in reproduction in PCOS-affected women as a potential cause of obesity and its accompanying signs and symptoms. Adipokines such TNFa, IL6, and IL1b have been thoroughly examined in the past and have a high correlation with infection [7].

Leptin

The Greek word leptos, meaning thin, gives rise to the name of the 167-amino acid protein leptin, which is encoded by the ob gene. It is a major hormone that regulates food intake, energy balance, and body weight. Leptin is the first discovered adipokine that has aided in the understanding of the functions of adipose tissue as a recognized source of energy and an essential endocrine organ in the body. Most leptin is secreted by adipose tissue. It is expressed by the pituitary, brain, stomach, placenta, and mammary gland [8].

According to Budak *et al*. (2006), adipocytes continuously produce leptin in proportion to their fat concentration. Because it quickly affects the hypothalamus to decrease food intake and increase energy expenditure, it is regarded as an anti-obesity hormone. Due to their rapid food consumption and enhanced fat synthesis, mice with a mutation in the leptin gene (ob gene), which results in the creation of the handiest defective and non-purposeful leptin, are considered genetically overweight (ob/ob mice) [9]. Gene alterations in the db/db mouse result in a phenotype that resembles fat and diabetes. Your leptin levels rise when you eat more and have less time to digest it. When leptin concentrations are high, your metabolism is switched to a more fatty track, which reduces the quantity of food you eat and boosts energy expenditure. According to Myers *et al*. (2010), patients with obesity who have elevated blood leptin levels are thought to be resistant to the hormone. Numerous processes, including aberrant affiliation with leptin-centered neural circuits, endoplasmic reticulum strain, and inadequate transport or signal to the brain, are linked to leptin resistance [10].

Leptin is crucial to keeping energy balance and has tremendous results on duplicate in women. Infertility and behind schedule puberty had been related to leptin or LEPR deficiency, the latter of which is resulting from a loss of function mutation within the gene accountable for people and mice. Additionally, leptin and its receptors are worried inside the usual progression of woman reproductive methods, along with lactation, the folliculogenesis, the ovarian improvement, the upkeep of the mammary gland's structure and characteristic, the maturation of the endometrium, the regulation of the menstrual cycle, and the endometrial receptivity, Figure 1 [11].

Resistin

Small and rich in cysteines, resistin is released as a polypeptide of 94 amino acids. Steppan *et al*. (2001) made the initial discovery of it while investigating how PPARg agonists affected glucose homeostasis. Because of this protein's "resistance to insulin" characteristic in mice, Steppan *et al*. dubbed it "resistin". This gene was subsequently given the Retn designation [12]. This adipokine was also identified by another group that same year, and because of its correlation with insulin resistance (IR) and its inhibitory influence on adipocyte development, it may be related to both diabetes and obesity. Mature white adipocytes in mice are the main source of resistin secretion [13].

Retinol-binding protein-4 RBP4

Protein 4, which is known as after the Greek letter omega, interacts with retinol. The protein referred to as RBP4 is typically produced via hepatocytes, however it is also produced by using adipocytes. It's been taken into consideration a new adipokine given that a take a look at of Glut4 mutants that were solely discovered in adipose tissue from 2005. Despite RBP4's function as a transporter of diet A (retinol), it has been identified as an adipokine that has an effect on glucose law and insulin sensitivity inside the systemic circulation. Figure 1. The attention of RBP4 is expanded in each humans and animals with insulin resistance [13]. However, additionally in this situation, serum RBP4 can motive inflammation. Systemic IR is triggered in mice by way of intraperitoneal management of human RBP4 recombinant protein. Conversely, the genetic removal of RBP4 will increase the sensitivity of insulin. The sensitivity of the peripheral part of the insulin device is inversely proportional to the level of RBP4 inside the plasma [14].

Chemerin

In 2003, the businesses Parmentier and Communi noticed chemerin, also referred to as the TIG2 or retinoic acid receptor responder 2 (RARRES2), a novel molecule that functions as a natural ligand for the orphan receptorchemR23 [15]. Nähemerin cleaves into its inactive counterpart upon irritation, releasing the active form. To achieve its potent leukocyte recruitment, chemerin uses its receptor ChemR23, a protein-coded seven-transmembrane receptor also known as a chemokine-like receptor 1 (CMKLR1). The main players in the expression of

ChemR23 are immature myeloid and plasmacytoid cells, monocytes, and natural killer cells (NK cells) (Parolini *et al*., 2007). ChemR1 has excessive specificity in its interactions with other G protein-coupled receptors (GPRs), such as GPR1 (Barnea *et al*. 2008) and C-C chemokine receptor-like 2 (CCLR2) [16]. Although there are many similarities between GPR1 and ChemR23, GPR1 expression in the liver, stomach, kidneys, and adipose tissue is generally different from ChemR23 expression. *In vivo*, the lung's endothelial cells exhibit high levels of CCLR2, whereas the liver's endothelial cells exhibit lower levels [17].

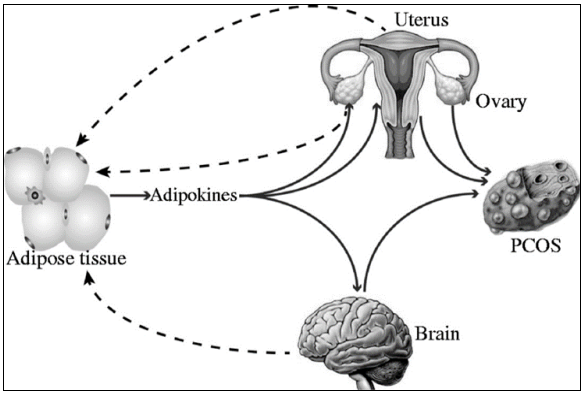

Fig 1: An association between adipokines and PCOS and obesity

Materials and Methods

The study was conducted from March 1st, 2024, until June 30th, 2024, at Teaching Tikit Hospital. There were 150 female patients in the trial, ranging in age from 15 to 45. following the completion of clinical and medical examinations by a physician who specializes in this area. In addition to selecting a random group, 75 samples of healthy females in the same age range as the control group were included.

Age, gender, weight, the patient's address, and a few other pertinent facts were used as each participant's input in the form of a multivariate dataset. An enzyme-linked immunosorbent test (ELISA) kit was used to measure the levels of serum Leptin, Resistin, Retinol binding protein-4, and Chemerin.

Statistical Analysis

The statistical program SPSS 25.0 (IBM Corp.) was used for the analyses. Prior to statistical analysis, variables with a skewed distribution underwent a logarithmic transformation. Using independent-samples t-tests, differences between the PCOS and control groups were evaluated. Minitab, a statistical program, was used to do the statistical analysis. One-way analysis of variance (ANOVA) was used to compare groups, and Duncan's multiple range test was used to look at the arithmetic means for parameters in order to identify significant differences, especially between groups. The Pearson correlation coefficient (R) between irisin and other parameters was presented using regression graphs. According to Popović (2021), the statistical significance criteria was found to be $p \geq 0.01$ [18].

Results

Table 1 displays the amounts of adipokines in PCOS patients as well as a control group. Figures 2, 3, 4, and 5 display averages with standard deviations. The patients' mean ± SD leptin concentrations were determined to be 201.50±19.2 pg/ml, while the control group's levels were 168.70±11.32 pg/ml. The average value for the test groups that were utilized to determine these values was 0.001, or the p-value.

According to mean and standard deviation values, the patients' and controls' resistin levels were 6.32±1.31 ng/ml and 3.65±2.16 ng/ml, respectively. The average value for the test groups that were utilized to determine these values was 0.044, or the p-value. The mean and standard deviation values of Retinol Binding Protein 4 were observed to be 45.1±24.0 ng/ml and 33. 5±18.4 ng/ml, respectively, for the patient and control groups. The average p-value for the test groups that were utilized to determine these results was 0.0003. According to mean and standard deviation values, the chemerin levels in the patients were 123.1±16.3 ng/ml and 76. 85±5.4 ng/ml, respectively, in the controls. The average value for the test groups that were utilized to determine these values was 0.002, or the p-value.

Table 1: The arithmetic average of the examined groups' adipokine concentrations

Groups	Leptin (pg/ml)	Resistin (ng/ml)	RBP4 (ng/ml)	Chemerin (ng/ml)
	Mean ± S.D	Mean ± S.D	Mean ± S.D	Mean ± S.D
P, N=150	201.50±19.2	6.32±1.31	45.1±24.0	123.1±16.3
C, N=75	168.70±11.32	3.65±2.16	33. 5±18.4	76. 85±5.4
P-Value	P0.001** = 0.0008**	0.044*	P = 0.0003**	0.002**

Note: P, PCOS patients, and healthy people make up C (Control). The potential thresholds are $p \leq 0.01$ (**), $p \leq 0.05$, and $p \geq 0.05$ (*), in that order.

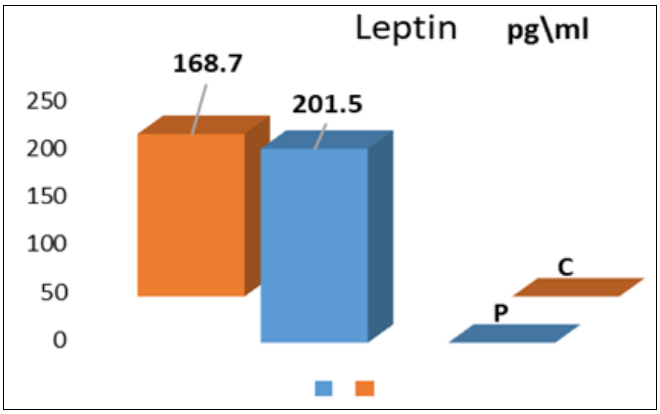

Fig 2: The leptin concentrations in the patient and control groups varied by pg/ml

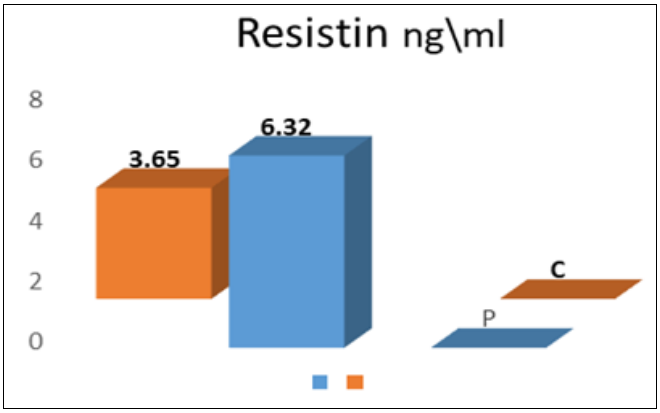

Fig 3: The resistin concentrations in the patient and control groups both displayed a range of ng/ml

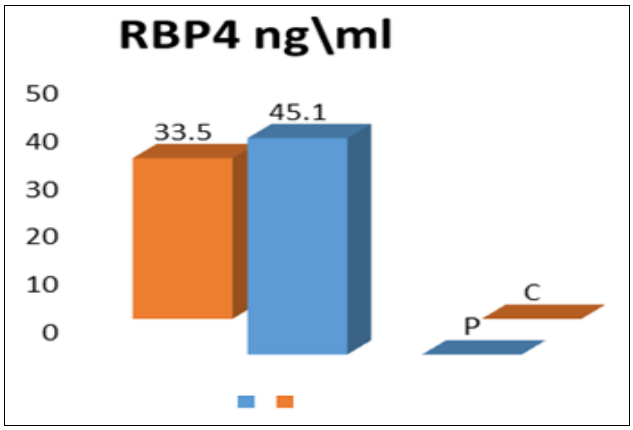

Fig 4: RBP4 values ranged from ng/ml in both the patient and control groups

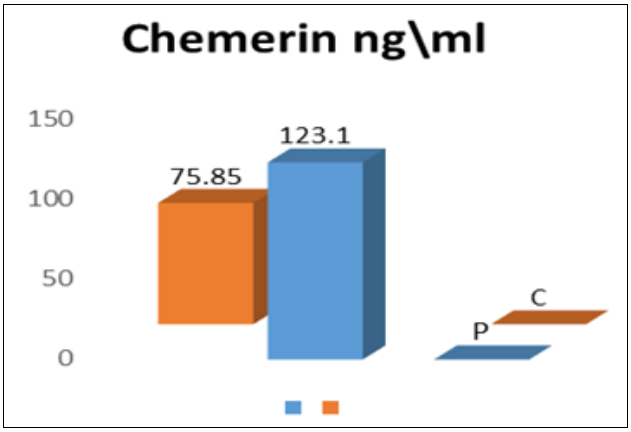

Fig 5: Chemerin concentrations ranged from ng/ml in both the patient and control groups.

Table 2: The correlation coefficient (R) between measures in PCOS patients

Parameters	Statistical Variables	Leptin	Resistin	RBP4	Chemerin
Chemerin	R	0.700	0.47	-0.19	
	P	0.000**	0.000**	0.541ns	
RBP4	R	-0.643	0.376		
	P	0.000**	0.033*		
Resistin	R	0.58			
	P	0.000**			

R: Correlation coefficient; P: p-value;* P≤0.05;** P≤0.01; NS: Not significant

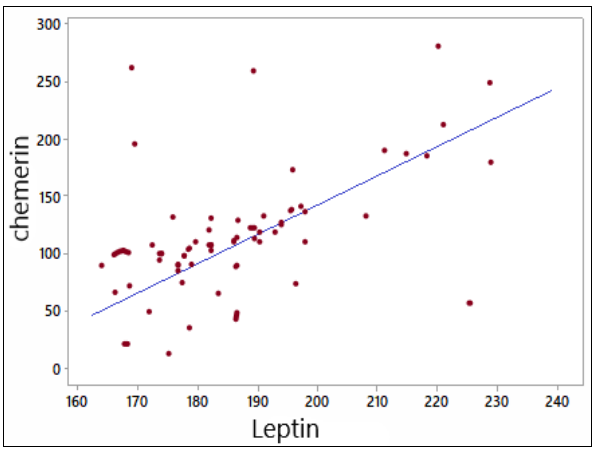

Fig 4: Leptin and Chemerin Correlation in Patients with PCOS

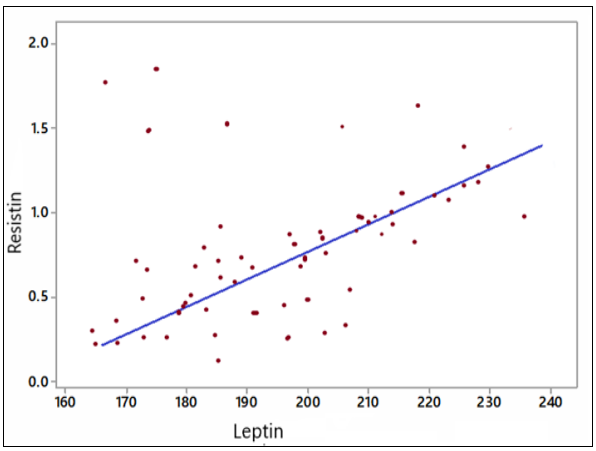

Fig 5: Leptin and Resistin Correlation in Patients with PCOS

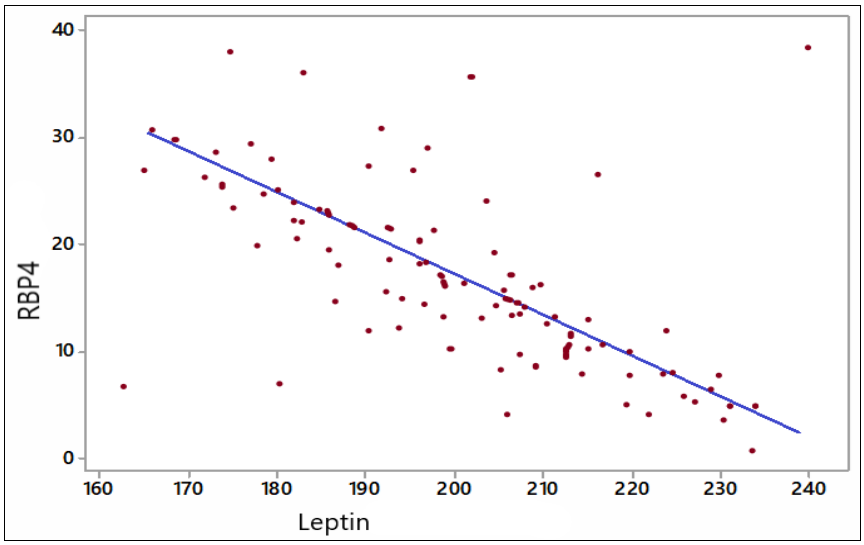

Fig 5: The association between leptin and RBP4 in patients with PCOS

Discussion

The first investigation on leptin and its signal in PCOS was published in 1996 [19], two years after the molecule's discovery [20]. The study's findings have indicated that in certain cases of PCOS, there may be an imbalance in the reproductive system's leptin signal. Subsequent studies have made an effort to investigate leptin's possible connection to PCOS. It is widely acknowledged that blood leptin levels and body fat percentage and mass index are related. Furthermore, the ratio of E2/SHBG, the level of E1/SHBG, and androgen or estrogen molecules are linked to leptin levels. Nevertheless, in PCOS patients or controls, no meaningful correlation was found between leptin and testosterone or androstenedione. The ongoing debate over whether blood leptin levels in PCOS patients vary from controls is displayed in Table 1. Compared to controls who are of comparable weight, women with PCOS have blood levels of leptin that are greater [21]. Furthermore, Wang *et al*. (2012) reported that obese PCOS patients' subcutaneous tissue exhibited greater levels of leptin mRNA than the controls. However, most studies have not shown a substantial difference in blood leptin levels between women with PCOS and age- and weight-matched controls [22]. Furthermore, there were no discernible variations in the blood levels of leptin between ovulatory and non-ovulatory individuals [23]. Furthermore, a recent study found that neither the expression of adipose leptin nor the levels of plasma leptin were impacted by PCOS [24]. These contradictory findings might be explained by the wide range of ethnicities and sample techniques employed in the adipose tissue biopsies research. Furthermore, it was discovered that PCOS had no connection to the leptin gene's G19A single nucleotide polymorphism [25]. It appears that low-dose oral contraceptives or the combination of estrogen and anti-androgen medication do not negatively impact the blood level of leptin in women with PCOS. Obesity and IR are common symptoms of PCOS. Since adipose tissue is the primary source of leptin, determining if IR in PCOS is correlated with serum leptin levels would be interesting. Between the PCOS-IR group and the PCOS-non-IR institution, there have been no discernible changes in the blood levels of either leptin or LEPR [26]. Yildizhan *et al*. (2011) found a relationship between IR and blood leptin levels in younger PCOS-afflicted women. One drug that fights both IR and hyperinsulinemia is troglitazone. Troglitazone therapy doesn't seem to affect leptin levels [27]. In contrast, all PCOS patients with PCOS who were overweight or non-obese and received metformin an insulin sensitizer that is often used to treat type 2 diabetes saw a decrease in their blood leptin levels [28]. Thus, there is ongoing disagreement over the relationship between IR and leptin. Future studies should elucidate the relationship between insulin resistance and leptin in PCOS-affected patients. The PCOS phenotype is somewhat but significantly impacted by the genetic polymorphism in the HPG axis [29]. As was already noted, leptin can affect reproduction by changing how the ovaries and the central part of the HPG axis work. Whether or if the HPG axis' control of leptin is to blame for the PCOS phenotype is a matter of concern. The frequency of leptin pulses and the length of the synchronization in PCOS patients and healthy women are noticed in the study by Sir-Petermann *et al*. (1999). Therefore, it does not seem that the leptin waveform is unique to PCOS. More research is required to ascertain the actual significance of the epigenetic relationship between LH and leptin. Because it regulates the ovary's steroidogenesis, insulin resistance, and reproductive-nerve axis, leptin has an indirect impact on the development and course of PCOS [30]. In particular, there are many variations in the LEPR gene that cause obesity to be inherited; these variants also increase the likelihood of developing PCOS. On the other hand, genetic variations in the LEP gene that encourage the inheritance of obesity and serve as risk factors for the onset of PCOS are one way that the transmission of obesity can negatively impact the epigenome. To completely understand the complex link between leptin and this illness, further molecular study is needed [31].

Rats with IR and T2DM have been related to resistin because circulation levels of resistin are elevated by dietary and hereditary obesity, as well as by the antidiabetic medication rosiglitazone. Perinatal blood mononuclear cells appear to be the main source of resistin in humans. By vying with lipopolysaccharide for binding to Toll-like receptor 4, it takes part in inflammatory processes. Resistin is not expressed in adipocytes but is substantially expressed in adipose tissue in humans. This is not the result of the adipocytes themselves, but rather of the existence of stromal cells and macrophages. Resistance gene expression is highly expressed in human preadipocytes; however, when the cells undergo induced transition into adipocytes, its expression declines. Resistin and IR have a complicated interaction in humans. This is still up for debate since some studies have linked resistin to IR in a favorable way, while other investigations have shown no correlation between resistin levels and IR, diabetes, or obesity. A protein called resistin is released into the bloodstream and acts in both endocrine and paracrine ways. It has been demonstrated to function as an AMPK inhibitor in the liver and muscles of mice; this lowers the amount of gluconeones produced in the liver and increases the absorption of glucose by the muscles. Additionally, resistin has been demonstrated to upregulate the production of SOCS-3, a recognized anti-inflammatory cytokine that has been seen to deactivate insulin signaling in a number of mice adipose tissue areas. By activating the p38 mitogen-activated protein kinase pathway and suppressing the insulin signal in primary human aortic endothelial cells, resisting increases the expression of phosphatases and tensin homologue deleted on chromosome 10. New details regarding potential mechanisms of resistin action in the genesis of adipocytes and the development of IR were provided by the findings of Sanchez-Solana *et al*. (2012), who reported that mouse resistin is a ligand for the tyrosine kinase-like orphan receptor ROR1, controlling expression of SOCS-3, the glucose transporter 4 (GLUT4), and GLUT1. It has been shown that resistin mRNA is present in the rat testis, cow ovaries, and hypothalamic-pituitary axis. Additionally, rat adipose tissue and macrophages have been reported to have it. Additionally, resistin is thought to be involved in the synthesis of steroid hormones as well as the growth of granulosa cells in rats and cattle. In spite of this, there was no discernible difference in the serum APN levels between obese and normal-weight women. Seow (2004) reported and other research have confirmed that there are no appreciable variations in the concentrations of serum or follicular fluid resistin between the PCOS group and the control group. Regardless of whether a woman had PCOS or was in the control group, Escobar-Morreale *et al*. (2006)

found that the amount of resistin in the blood was greater in overweight and obese women than in lean women.

Since the adipocyte is not the body's major source of resistin, the resistin generated by adipocytes does not appear to play a substantial function *in vivo*. On the other hand, PCOS adipocytes had far greater resistin mRNA levels than normal control cells. Following laparoscopic ovarian electroporation, it was shown that both obese and lean women with PCOS had reduced expression of the adipocyte-specific gene resistin. Furthermore, no discernible variations were seen in the resistin levels in plasma between the PCOS-IR and PCOS-non-IR groups. Nonetheless, Munir *et al*. found that mean serum resistin concentration and testosterone were positively correlated, with the latter rising by 40% in PCOS patients in 2005. Furthermore, it has been shown that the combination of resistin and insulin increases the production of androgen in the ovaries by activating the gene that produces 17x hydroxylase in the theca cells of the ovary. There was no significant correlation found in the resistin promoter studies between the PCOS traits and the promoter variations of the resistin gene. (Urbanek and others, 2003).

Contrarily, resistin gene variants were linked to body mass index in women with PCOS, indicating that obesity and the resistin gene are connected in PCOS patients. In a randomized, double-blind, placebo-controlled study, rosiglitazone was shown to significantly enhance circulating serum resistin levels in obese PCOS women, therefore confirming its potential to boost insulin's ability to slow down the progression of the condition. Thus, resistin is likely to be one of the most significant adipokines associated with obesity, insulin resistance, and PCOS. It was discovered that RBP4 and obesity are related.

In the subcutaneous and visceral regions of the adipose tissue, this comparison revealed higher levels of RBP4 in the circulation and tissue expression of RBP4 in lean vs overweight participants. Following dietary intervention for weight loss, serum RBP4 levels dropped; the drop was more pronounced when a low-carb diet was followed. RBP4 mRNA, proteins, and secretion into the medium of human adipose tissue from the subcutaneous and omental areas were all elevated by 17β-estradiol. DHEA-S 44, insulin, androstenedione, or testosterone did not alter the expression of RBP4. There aren't many, if any, research that have thoroughly examined RBP4's possible involvement in the pathophysiology of PCOS. Comparing PCOS patients with controls revealed a substantial rise in RBP4 blood levels [45]. According to a different research, obese or overweight women with PCOS had greater blood levels of RBP4 than age- and weight-matched controls. Furthermore, as compared to controls, the subcutaneous and omental adipose tissues of obese women with PCOS had considerably higher levels of RBP4 mRNA [46]. There was no correlation found between RBP4 and IR in PCOS-affected women. RBP4 levels, however, showed a significant correlation with both TG and LH. Furthermore, there were no discernible variations in blood RBP4 concentrations between ovulatory and non-ovulatory women. In the current investigation, women with PCOS who underwent controlled ovarian hyperstimulation in order to facilitate IVF embryo transfer showed a noteworthy reduction in the level of RBP4 in their bloodstream. The characteristics or results of in vitro fertilization did not correlate with serum levels of RBP4. It's also noteworthy that retinoids, such as retinol and its derivatives, have been shown to modify androgen and steroidogenic enzyme expression in both normal and PCOS theca cells. Moreover, Wickenheisser *et al*. showed that retinol only enhanced CYP17 mRNA expression and promoter activity in PCOS patients-not in healthy human theca cells. This discovery may help to explain why theca cells in PCOS-affected women produce an excessive amount of androgens [50]. Measuring the hepatic levels of RBP4, a protein that carries retinol from the liver to other tissues, might be interesting in this regard. In fact, a statistical correlation between greater RBP4 levels and PCOS-afflicted women compared to controls was discovered [51]. To fully understand the connection between retinol, RBP4, and increased testosterone production in PCOS-affected women, further research is necessary. According to a notion put out, the concentration of bioactive chemerin is raised locally, which is consistent with the idea that chemerin and CMKLR1 interact with other cells.

Chemerin has been connected to adipogenesis, adipocyte metabolism, and glucose metabolism in addition to immunity. The cytokine has been dubbed a novel adipokine because of its high concentration in white adipocytes, and illnesses linked to it include obesity, metabolic syndrome, and type 2 diabetes 53. Bozaoglu and his colleagues documented this phenomena in a research that was published in Science. Lechner *et al*. found a substantial association between blood pressure and plasma chemerin concentration, BMI, and plasma triglycerides, as would be expected. Conversely, it has been documented that chemerin has the ability to control insulin secretion as well as the sensitivity of the insulinotropic axis. On the other hand, it has also been demonstrated that insulin causes adipocytes to produce more chemerin. Human umbilical cord blood has also been demonstrated to contain chemerin during reproduction. The increase in decidual chemerin in the early stages of pregnancy may contribute to changes in the nature of the vascular network and the quantity of NK cells. Chemerin was found in the rat placenta, and as pregnancies go on, the amount of chemerin in the serum drops, according to a 2012 study by Garces *et al*. These results suggested that chemerin could play a major part in preserving metabolic stability and balance during pregnancy. Chemerin mRNA levels in PCOS patients' blood, subcutaneous, and omental tissues were significantly higher at this period. Significant reductions in serum chemerin levels were also observed in PCOS patients after six months of metformin treatment. The rat model of PCOS generated by 5a-dihydrotestosterone showed significantly increased levels of the adipokine chemerin and its receptor ChemR23 in its ovaries. Notably, chemerin can have a deleterious impact on the follicular estrogen synthesis that is triggered by FSH.

Conclusion

Patients with PCOS are frequently overweight, which both independently and significantly exacerbates the condition. Adipokines, which are generated by adipose tissue and may have an impact on a woman's reproductive processes and metabolic characteristics, are the means by which adipose tissue interacts with the brain, ovaries, and uterus (Figure 1). The varied amounts of adipokines in PCOS patients have suggested the molecules' role in PCOS pathology; however, because of inconsistent findings from different research, the majority of the molecules have not yet been identified in

PCOS. Additionally, centrally located increases in abdominal fat deposits are linked to PCOS, regardless of the presence of obesity. Additionally, PCOS may adversely affect adipokine secretion; this is true for women regardless of their level of obesity. As a result, adipokines may constitute a type of endocrine cross-talk between obesity and PCOS, as schematically shown in Figure 1. Finally, it's important to keep in mind that most research has tried to connect the amounts of adipokines in circulation. Whether all adipokines have a real endocrine role is still up for debate. Adipokine levels in the blood may not accurately represent events brought about by autocrine or paracrine mechanisms at the tissue level. The majority of research conducted thus far have not made use of blood-based measures. Furthermore, it has not been shown that adipokines are suitable for proteomics or genomic analysis of human omental adipose tissue in PCOS. It's still unclear how adipokines fit into the pathophysiology of PCOS. Because of the vast range of clinical symptoms linked to endocrine, metabolic, and reproductive problems, PCOS is very difficult to investigate. Therefore, more investigation is required to elucidate the mechanism by which adipokines function in reproductive processes, perhaps serving as a mediator between obesity and PCOS. According to the aforementioned research, adipokines may have a role in the onset of PCOS.

References

1. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: Etiology, pathogenesis and diagnosis. Nat Rev Endocrinol. 2011;7(3):219-31.
2. Bauer S, Bala M, Kopp A, Eisinger K, Schmid A, Schneider S, *et al*. Adipocyte chemerin release is induced by insulin without being translated to higher levels *in vivo*. Eur J Clin Invest. 2012;42(6):1213-20.
3. Kandarakis DE, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev. 2012;33(7):981-1030.
4. Möhlig M, Flöter A, Spranger J, Weickert MO, Schill T, Schlösser HW, *et al*. Predicting impaired glucose metabolism in women with polycystic ovary syndrome by decision tree modelling. Diabetologia. 2006;49:2572-9.
5. Livadas S, Anagnostis P, Bosdou JK, Bantouna D, Paparodis R. Polycystic ovary syndrome and type 2 diabetes mellitus: A state-of-the-art review. World J Diabetes. 2022;13(1):5-26.
6. Yildiz BO, Bozdag G, Otegen U, Harmanci A, Boynukalin K, Vural Z, *et al*. Visfatin and retinol-binding protein 4 concentrations in lean, glucose-tolerant women with PCOS. Reprod Biomed Online. 2010;20(9):150-155.
7. Carmina E, Campagna AM, Lobo RA. A 20-year follow-up of young women with polycystic ovary syndrome. Obstet Gynecol. 2012;119(4):263-269.
8. Vasselli JR, Scarpace PJ, Harris RB, Banks WA. Dietary Components in the Development of Leptin Resistance. Adv Nutr. 2013;4:164-175.
9. Russo B, Menduni M, Borboni P, Picconi F, Frontoni S. Autonomic Nervous System in Obesity and Insulin-Resistance-The Complex Interplay Between Leptin and Central Nervous System. Int J Mol Sci. 2021;22:5187. DOI: 10.3390/ijms22105187.
10. Zhao S, Zhu Y, Schultz RD, Li N, He Z, Zhang Z, *et al*. Partial Leptin Reduction as an Insulin Sensitization and Weight Loss Strategy. Cell Metab. 2019;30:706-719.
11. Moghetti P, Tosi F. Insulin Resistance and PCOS: Chicken or Egg? J Endocrinol Invest. 2021;44:233-244.
12. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA. The hormone resistin links obesity to diabetes. Nature. 2001;409:307-312.
13. Azuma K, Oguchi S, Matsubara Y, Mamizuka T, Murata M, Kikuchi H, *et al*. Novel resistin promoter polymorphisms: association with serum resistin level in Japanese obese individuals. Horm Metab Res. 2004;36(7):564-570.
14. Piltonen T, Puurunen J, Hedberg P, Ruokonen A, Mutt SJ, Herzig KH, *et al*. Oral, transdermal and vaginal combined contraceptives induce an increase in markers of chronic inflammation and impair insulin sensitivity in young healthy normal-weight women: A randomized study. Hum Reprod. 2012;27:3046-3056.
15. Hudecova M, Holte J, Olovsson M, Sundstrom Poromaa I. Long-term follow-up of patients with polycystic ovary syndrome: Reproductive outcome and ovarian reserve. Hum Reprod. 2009;24:1176-1183.
16. Tal S, Seifer DB, Arici A. The emerging role of angiogenic factor dysregulation in the pathogenesis of polycystic ovarian syndrome. Semin Reprod Med. 2015;33:195-207.
17. Anusha S, Mayank C, Puran B, Amitabh K. Adiponectin and chemerin contrary adipokines in regulating reproduction and metabolic disorders. Reprod Sci. 2018;25:1462-1473.
18. Popović BV. Understanding advanced statistical methods. J Appl Stat. 2021;41(12):27-77.
19. Brzechffa PR, Jakimiuk AJ, Agarwal SK, Weitsman SR, Buyalos RP, Magoffin DA. Serum immunoreactive leptin concentrations in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 1996;81(8):4166-4169.
20. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994;372(87):425-432.
21. Vicennati V, Gambineri A, Calzoni F, Casimirri F, Macor C, Vettor R, *et al*. Serum leptin in obese women with polycystic ovary syndrome is correlated with body weight and fat distribution but not with androgen and insulin levels. Metabolism. 1998;47(43):988-992.
22. Wang L, Li S, Zhao A, Tao T, Mao X, Zhang P, *et al*. The expression of sex steroid synthesis and inactivation enzymes in subcutaneous adipose tissue of PCOS patients. J Steroid Biochem Mol Biol. 2012;132:120-126.
23. Abruzzese GA, Gamez J, Belli SH, Levalle OA, Mormandi E, Otero P, *et al*. Increased chemerin serum levels in hyperandrogenic and normoandrogenic women from Argentina with polycystic ovary syndrome. Gynecol Endocrinol. 2020;36:1057-1061.
24. Ożegowska K, Wieczorek BJ, Bogacz A, Mrozikiewicz SA, Duleba AJ, Pawelczyk L. Relationship between adipocytokines and angiotensin converting enzyme gene insertion/deletion polymorphism in lean women with and without polycystic ovary syndrome. Gynecol Endocrinol. 2019;36(5):1-5.

25. Reverchon M, Cornuau M, Rame C, Guerif F, Royere D, Dupont J. Chemerin inhibits IGF-1-induced progesterone and estradiol secretion in human granulosa cells. Hum Reprod. 2012;27:1790-800.
26. Foda AA, Foda EA, El-Negeri MA, El-Said ZH. Serum chemerin levels in polycystic ovary syndrome after metformin therapy. Diabetes Metab Syndr. 2019;13:1309-1315.
27. Yildizhan R, Ilhan GA, Yildizhan B, Kolusari A, Adali E, Bugdayci G. Serum retinol-binding protein 4, leptin, and plasma asymmetric dimethylarginine levels in obese and nonobese young women with polycystic ovary syndrome. Fertil Steril. 2011;96(8):246-50.
28. Cekmez F, Cekmez Y, Pirgon O, Canpolat FE, Aydinöz S, Ipcioglu MO, *et al*. Evaluation of new adipocytokines and insulin resistance in adolescents with polycystic ovary syndrome. Eur Cytokine Netw. 2011;22(8):32-43.
29. Kennedy AJ, Davenport AP. International union of basic and clinical pharmacology CIII chemerin receptors CMKLR1 (Chemerin1) and GPR1 (Chemerin2) nomenclature, pharmacology, and function. Pharmacol Rev. 2018;70(6):174-196.
30. Pelanis R, Mellembakken JR, Poromaa SI, Ravn P, Papunen ML, Tapanainen JS, *et al*. The prevalence of Type 2 diabetes is not increased in normal-weight women with PCOS. Hum Reprod. 2017;32:2279-2286.
31. Catteau A, Caillon H, Barrière P, Denis MG, Masson D, Fréour T. Leptin and Its Potential Interest in Assisted Reproduction Cycles. Hum Reprod Update. 2016;223:320-341.
32. Seow KM, Juan CC, Wu LY, Hsu YP, Yang WM, Tsai YL, *et al*. Serum and adipocyte resistin in polycystic ovary syndrome with insulin resistance. Hum Reprod. 2004;19(1):48-53.
33. Livadas S, Anagnostis P, Bosdou JK, Bantouna D, Paparodis R. Polycystic ovary syndrome and type 2 diabetes mellitus: A state-of-the-art review. World J Diabetes. 2022;13(1):5-26.
34. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, *et al*. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Hum Reprod. 2014;45(5):1239-1247.
35. Amato MC, Vesco R, Vigneri E, Ciresi A, Giordano C. Hyperinsulinism and polycystic ovary syndrome (PCOS): role of insulin clearance. J Endocrinol Invest. 2015;38(8):1319-1326.
36. Pasquali R, Victorin SE, Yildiz BO, Duleba AJ, Hoeger K, Mason H, *et al*. PCOS Forum: research in polycystic ovary syndrome today and tomorrow. Clin Endocrinol. 2011;74(4):424-433.
37. Kochan Z, Karbowska J. Dehydroepiandrosterone up-regulates resist in gene expression in white adipose tissue. Mol Cell Endocrinol. 2004;218(2):57-64.
38. Sanchez-Solana B, Laborda J, Baladron V. Mouse resistin modulates adipogenesis and glucose uptake in 3T3-L1 preadipocytes through the ROR1 receptor. Mol Endocrinol. 2012;26:110-27.
39. Morreale EHF, Villuendas G, Carretero BJI, Blasco AF, Sanchon R, Luque-Ramirez M, San Millan JL. Adiponectin and resistin in PCOS: A clinical, biochemical and molecular genetic study. Hum Reprod. 2006;21:2257-2265.
40. Munir I, Yen HW, Baruth T, Tarkowski R, Azziz R, Magoffin DA, *et al*. Resistin stimulation of 17a-hydroxylase activity in ovarian theca cells in vitro: relevance to polycystic ovary syndrome. J Clin Endocrinol Metab. 2005;90(7):4852-4857.
41. Chen MJ, Chen HF, Chen SU, Ho HN, Yang YS, Yang WS. The relationship between follistatin and chronic low-grade inflammation in women with polycystic ovary syndrome. Fertil Steril. 2009;92(6):2041-2044.
42. Zheng SH, Du DF, Li XL. Leptin levels in women with polycystic ovary syndrome: A systematic review and a meta-analysis. Reprod Sci. 2017;24(5):656-670.
43. Jia J, Bai J, Liu Y, Yin J, Yang P, Yu S, *et al*. Association between retinol-binding protein 4 and polycystic ovary syndrome: A meta-analysis. Endocr J. 2014;45(80):114-186.
44. Arikan Ş, Bahceci M, Tuzcu A, Kale E, Gökalp D. Serum resistin and adiponectin levels in young non-obese women with polycystic ovary syndrome. Gynecol Endocrinol. 2010;26(3):161-166.
45. Nambiar V, Vijesh VV, Lakshmanan P, Sukumaran S, Suganthi R. Association of adiponectin and resistin gene polymorphisms in South Indian women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol. 2016;200:82-88.
46. Chu Y, Cui Q, Feng G, Song Z, Jiang X. The expression of resistin in adipose tissues of patients with polycystic ovary syndrome and insulin resistance. J Huazhong Univ Sci Technolog Med Sci. 2009;29(5):642.
47. Wickenheisser JK, DeGrave NVL, Hendricks KL, Legro RS, Strauss JF III, McAllister JM. Retinoids and retinol differentially regulate steroid biosynthesis in ovarian theca cells isolated from normal cycling women and women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2005;90:4858-4865.
48. Wood JR, Ho CK, Nelson-DeGrave VL, McAllister JM, Strauss JF III. The molecular signature of polycystic ovary syndrome (PCOS) theca cells defined by gene expression profiling. J Reprod Immunol. 2004;63:51-60.
49. Garcia MMA, Moncayo S, Insenser M, Blasco AF, Ramirez LM, Morreale EHF. Metabolic cytokines at fasting and during macronutrient challenges: influence of obesity, female androgen excess and sex. Nutrients. 2019;11(8):2566-2576.
50. Goralski KB, McCarthy TC, Hanniman EA, Zabel BA, Butcher EC, Parlee SD, *et al*. Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. J Biol Chem. 2007;282:28175-28188.
51. Bozaoglu K, Bolton K, McMillan J, Zimmet P, Jowett J, Collier G, *et al*. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology. 2007;148:4687-4694.
52. Foda AA, Foda EA, El-Negeri MA, El-Said ZH. Serum chemerin levels in polycystic ovary syndrome after metformin therapy. Diabetes Metab Syndr. 2019;13:1309-1315.
53. Garces MF, Sanchez E, Acosta BJ, Angel E, Ruiz AI, Rubio-Romero JA, Dieguez C, Nogueiras R, Caminos JE. Expression and regulation of chemerin during rat pregnancy. Placenta. 2012;33:373-378.
54. Kabiri N, Tabandeh M, Tabatabaie SR. Beneficial effects of pioglitazone and metformin in murine model of polycystic ovaries via improvement of chemerin

gene up-regulation. DARU. 2014;67(4):22-39.
55. Chapman IM, Wittert GA, Norman RJ. Circulating leptin concentrations in polycystic ovary syndrome: relation to anthropometric and metabolic parameters. Clin Endocrinol. 1997;46:175-181.

How to Cite This Article
Ahmed RH. Adipocytokines as a fertility factor: A connection between obesity and PCOS (Polycystic Ovary Syndrome). International Journal of Obstetrics and Gynaecological Nursing. 2024;6(2):184-192.

Creative Commons (CC) License
This is an open-access journal, and articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 International (CC BY-NC-SA 4.0) License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.