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Galanin-Like Peptide's Association with Insulin Resistance in PCOS Patients

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ABSTRACT

Background: Women in the reproductive age range are susceptible to the common complex endocrine condition known as polycystic ovarian syndrome, or PCOS. It has been demonstrated that galanin-like peptide (GALP) is linked to ovulation regulation.

Objectives: The purpose of this study was to evaluate women with polycystic ovarian syndrome (PCOS) for reduced blood levels of Galanin-like peptide (GALP) and serum insulin resistance.

Patients and methods: In this study, 40 healthy women who were age-matched to the PCOS patients were selected as the control group, while 100 women with PCOS between the ages of 15 and 45 took part: A cross-sectional study was conducted at Kirkuk City's hospitals and outpatient clinics between September and December 2024.Patients with PCO are diagnosed using the Rotterdam criteria. Participants were recruited after completing informed consent and having all eligibility requirements confirmed. The body mass index is computed both prior to and following treatment. The insulin resistance homeostatic model evaluation is calculated using the formula below.: An ELISA kit was used to assess the ratio of fasting insulin to fasting glucose by 405 galanin-like peptide (GALP) in human serum using the Enzyme-Linked Immunosorbent Assay technique. An automatic biochemical analyzer was used to assess the levels of triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC). SPSS for Windows 7 was utilized for data analysis.

Results: This group's serum levels of human GALP (galanin-like peptide) were considerably ($p>0.01$) lower than those of the control group. Serum levels of LDL and total cholesterol in PCOS patients were significantly higher than those in the control group ($p>0.01$). The serum levels of HDL, VLDL, and triglycerides are non-significant (p-value >0.05). Furthermore, compared to the control group, there was a substantial ($p>0.01$) rise in serum glucose and HOM-IR levels in PCOS patients.

Conclusion: Women with PCOS had lower serum levels of human GALP (galanin-like peptide) than the control group.

Keywords: *PCOS, Insulin resistance, Galanin-like peptide , LDL, Total cholesterol, Lipid profile.*

1. INTRODUCTION

Polycystic ovarian syndrome, or PCOS, is the most prevalent endocrinopathy in the world among women of reproductive age. There is a wide range of symptoms associated with the condition; some people just experience minor ones, while others have major disruptions in their metabolic, endocrine, and reproductive systems. PCOS was initially described in greater detail by Stein and Leventhal in 1935 (1).

In humans and other mammals, the neuropeptide galanin-like peptide (GALP) is found. This 60 amino acid polypeptide is produced by the posterior pituitary gland and the arcuate nucleus of the hypothalamus. Along with controlling appetite, it may also have an impact on stress, inflammation, and sexual behavior [(2)].

The findings also suggest that GALP may play a role in energy metabolism because of its ability to maintain continuous stimulation of the sympathetic nervous system (SNS) through thermogenesis, the process by which heat is generated within living organisms. The fact that thyroid-stimulating hormone (TSH) output falls when GALP is directly injected into the brain lends more credence to the notion that GALP contributes to energy balance. This implies that the neuroendocrine regulation of the hypothalamic-pituitary-thyroid (HPT) axis involves GALP [(3)].

Although the precise etiology of PCOS is unknown, it is thought to be a heterogeneous disorder with multiple contributing causes. Obesity, insulin resistance in skeletal muscles and adipose tissue as a result of a post-receptor

malfunction (abnormal phosphorylation of tyrosine kinase), and lower levels of follicle-stimulating hormone (FSH) in relation to LH are some of the underlying causes of PCOS and increased pulse frequency of gonadotrophin-releasing hormone (GnRH), which increases the frequency and amplitude of luteinizing hormone (LH) secretion and stimulates theca cells to produce androgen [4].

The aforementioned hypothesized underlying diseases in PCOS include elevated LH pulse frequency, elevated hypothalamic kisspeptin levels, and increased activity of the GnRH neural network. A shift in the body's metabolic state is probably partially to blame for this elevated hypothalamic GnRH production. Galanin (GAL) and ghrelin (GHRL), neuropeptide Y (NPY), and galanin-like peptide (GALP) have all been proposed as possible metabolic state messengers to the animal GnRH neural network [5].

The arcuate nucleus (ARC) contains a recently identified hypothalamic peptide termed GALP, which seems to enhance GnRH production by the hypothalamus and GT1-7 cells, a cell line of GnRH neurons (6). The neuropeptide GALP controls eating patterns, body weight, and energy metabolism. We want to look into serum GALP levels in PCOS patients, who have both metabolic and neurological activity, since neuroendocrine abnormalities are a contributing factor in the etiology of PCOS. Additionally, we sought to assess the relationship between blood GALP levels and serum indicators of cardiovascular disease risk, including vitamin D, metabolic parameters, hormonal profiles, and fibrinogen, D-dimer, and CRP, in both PCOS-affected and non-PCOS-affected individuals. Research on GALP levels in PCOS patients is not yet available in the literature [7].

Obesity increases insulin resistance. An improper reaction to insulin in metabolically active marginal tissues, such as skeletal muscle and adipose tissue, causes inherent insulin resistance in PCOS (8). Insulin resistance, which can result in improper glucose and lipid catabolism, is more common in obese women with PCOS. Moreover, raising insulin stimulates free androgens and lowers blood levels of sex hormone-binding globulin (SHBG), which prevents follicle formation and results in irregular menstruation and impotence. Female PCOS patients were substantially more likely to eat foods high in sugar, like white bread and fried potatoes. Numerous adipokines are released by the fatty tissues, and each one has a unique impact on insulin resistance. Other molecules, including visfatin, may have insulin-like activity and stimulate the insulin receptor, whereas adiponectin has an insulin-sensitizing effect (9). Adiponectin, a rich protein that comes in multimers, is released by the adipocyte. Included are molecular weights that are high, low, and intermediate. While some studies indicated a negative link between adiponectin levels and BMI, other studies identified an independent correlation between adiponectin and PCOS. These adipokines can be evaluated as markers of insulin resistance in PCOS patients regardless of BMI. Diabetes and heart disease can be slowed down by consuming fewer calories from total fats, saturated fats, and cholesterol. They affect the functioning of the ovaries (10). By stimulating the pituitary gland's insulin receptors to release luteinizing hormone, excessive insulin synthesis might exacerbate the ovary's and glands' androgen excretion. It raises free testosterone levels and might reduce hepatic SHBG synthesis. Alopecia and acne symptoms may result from excessive androgen excretion, which may also impede the development of ovarian follicles [11]

2. MATERIALS AND METHODS

Design of study

A cross-sectional study was conducted in the Kirkuk city hospitals and outpatient clinics during the period from September to December 2024.

Ethical consideration

The University of Tikrit's College of Medicine's scientific committee first recommended and then authorized the study. After extensively describing the purpose and methodology of the study and guaranteeing the anonymity and confidentiality of the responses, the patients verbally gave their fully informed consent.

Study population

Sampling method

The current study included 100 women with PCOS who were a convenient sample and were between the ages of 15 and 45. PCOS was diagnosed using the Rotterdam criteria, which included the following:

1. Anovulation or oligolibulation.

2. Hyperandrogenism's biochemical and/or clinical indicators,

3. The presence of at least 12 follicles, each measuring 2 to 9 mm, and/or an ovarian volume of at least 10 mL in at least one ovary are characteristics of polycystic ovarian morphology on transvaginal or abdominal ultrasound.

During the clinical examination, the researcher looked for the following clinical signs of PCOS: weight gain, particularly around the abdomen; Dark or thick patches of skin on the back of the neck, behind the breasts, and in the armpits; male-pattern baldness or thinning hair; acne or oily skin; and small bits of extra skin on the neck or armpits (skin tags).

A radiologist from Kirkuk General Hospital's Radiology Department and the Radiology Private Clinic in Kirkuk performed the ultrasound examination.

Inclusion criteria

According to the modified Rotterdam criteria, women who are newly diagnosed with PCOS must meet two requirements: they must exhibit medical and/or biochemical evidence of hyper-androgenism and have at least one of the following. A qualified gynecologist will use laboratory hormone testing, scientific points, and ultrasound examination to determine whether the ovaries are polycystic, oligo-, or anovulation.

Exclusion criteria

• Women with additional causes of hyperandrogenism, including Cushing's disease, androgen-secreting tumors, and congenital adrenal hyperplasia.

• Women with hyperprolactinemia who are infertile.

• Disfunction of the thyroid.

• Any history of ovarian surgery, early ovarian aging, or solid or cystic masses in the ovaries during the second to fourth days of menstruation.

• Women who were nursing or pregnant.

Sample Collection and Storage

Each individual had a vein punctured to get approximately 5 ml of blood. After being put into a sterile, straightforward tube, the blood pattern was left to coagulate at room temperature for ten to fifteen minutes. The serum pattern was then separated, placed into three clear, dry Eppendorf tubes, labeled with the quantity, and stored at -20 °C until it was needed for analysis. After that, the tube was centrifuged for ten minutes at 3000 rounds per minute (rpm).

Methods

Measurement of the Height and Weight

A diagnostic tool for assessing the prevalence of obesity in a population is the body mass index, or BMI. In this study, each patient's height and weight were recorded, and their BMI was calculated using the following formula:

BMI = Weight (kg) / Square height (m^2)

The BMI classification to measure obesity is according to WHO [12]

Measurement of Lipid profile [13,14]

Blood samples were taken to conduct a lipid examination after 8 hr fasting at least, and the group of cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, and very low-density lipoprotein were measured automatic biochemical analyzer.

Measurement of Insulin Resistance [15]

Insulin Resistance Measurement: IR repute was formerly determined using IR indices, such as the QUICKI ≤ 0.333 and 9k-iIR ≥ 2.5, which are now recognized as IR groups. These formulas used to be the sole basis for calculating the IR indices mentioned:

HOMA= [Fasting insulin (μIU/ml) × Fasting glucose (mg/dl)]/405.

3. RESULTS

Serum level of Galanin-like peptide in women with polycystic ovary syndrome (PCOS).

As shown in table (1), according to the presented data show the mean ± SD of the serum level of Galanin-like peptide in polycystic ovary syndrome (PCOS) comparing with the control group, the result was significant ($p<0.01$) reduction in serum level of Galanin-like peptide.

Table 1: Comparison between polycystic ovary syndrome (PCOS) and healthy women regarding the mean ± SD of Galanin-like peptide

Study groups	n	Galanin-like peptide (pg/mL) Mean ± SD	P. value

Polycystic Ovary syndrome (PCOS)	100	39.6±19.8	P<0.01
Control group	40	48.8 ± 16.8	significant

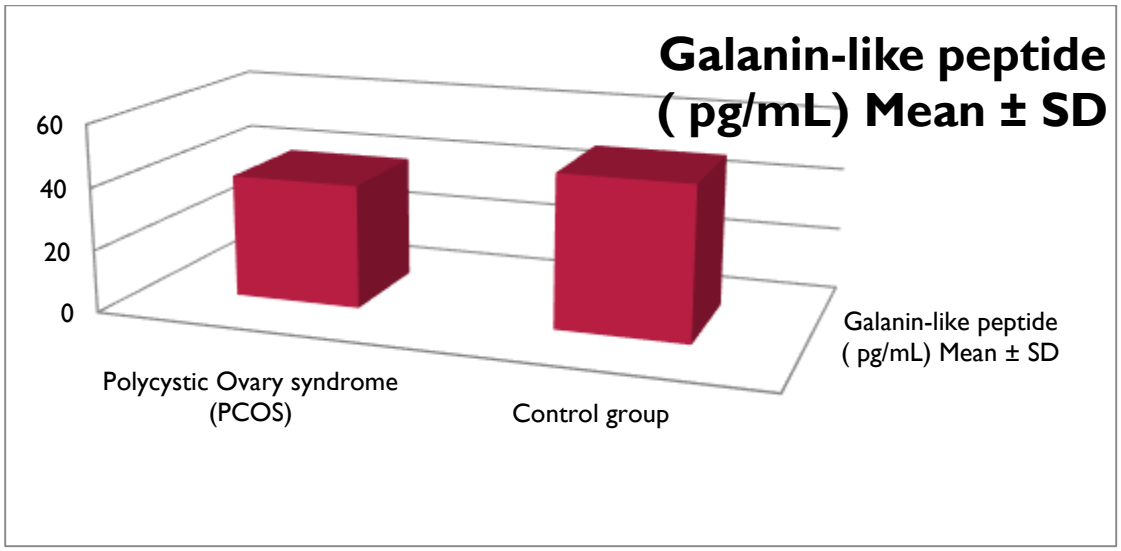

Fig. (1): Comparison between polycystic ovary syndrome (PCOS) and healthy women regarding the mean ± SD of Galanin-like peptide

2. Serum level of lipid profile in women with polycystic ovary syndrome (PCOS).

As shown in table (2), according to the presented data show the mean ± SD of the serum level of serum total cholesterol and LDL in polycystic ovary syndrome (PCOS) comparing with the control group the result was significant (p<0.01). There is a non-significant in serum level of (triglycerides, HDL, VLDL) at p-value >0.05.

Table 2: Comparison between polycystic ovary syndrome (PCOS) and healthy women regarding the mean ± SD of serum sex hormones (total cholesterol, triglycerides, HDL, LDL, VLDL).

Study groups	**Mean ± SD**				
	Total cholesterol mg/dl	**Triglycerides mg/dl**	**HDL mg/dl**	**LDL mg/dl**	**VLDL mg/dL**
Polycystic ovary syndrome (PCOS)	212.6±29.8	172.5±24.7	±7.2 37.4	122.0±24.6	33.7±5.6
Control group	±16.87 166	±33.2 168.7	38±5.6	92±13.5	31.5±3.9
P. value	0.01	0.955	0.763	0.01	0.9

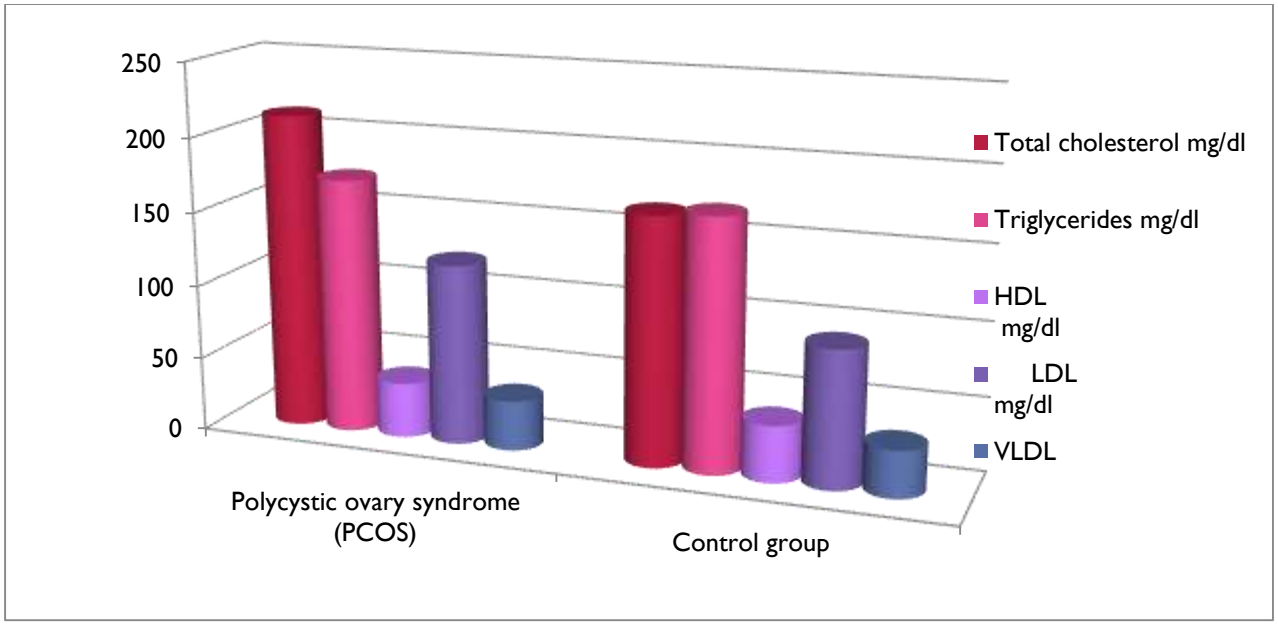

Fig. (2): Comparison between polycystic ovary syndrome (PCOS) and healthy women regarding the mean ± SD of serum lipid profile (total cholesterol, triglycerides, HDL, LDL, VLDL).

Level of serum glucose and Insulin Resistance in women with polycystic ovary syndrome (PCOS).

As shown in table (3), according to the presented data show the mean ± SD of the levels of serum glucose and insulin in polycystic ovary syndrome (PCOS) comparing with the control group, the results were significant ($p<0.01$) elevated of glucose and HOM-IR.

Table 3: Comparison between polycystic ovary syndrome (PCOS) and healthy women regarding the mean ± SD of serum glucose and Insulin Resistance.

Study groups	**N**	**Glucose (mg/dl) Mean ± SD**	**Homeostatic Model Assessment for Insulin Resistance HOM-IR ((u/l)) Mean ± SD**
Polycystic ovary syndrome (PCOS)	100	132.5 ± 18.4	3.5±1.3
Control group	40	± 19.1 100.0	2.0±1.6
P_{value}		<0.01	<0.01

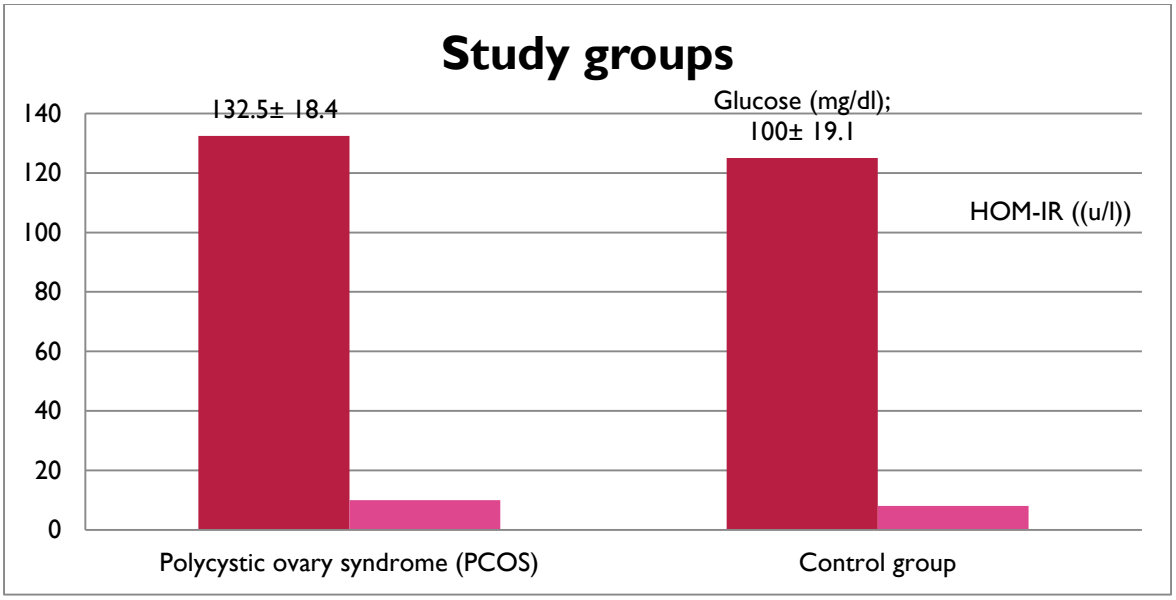

Fig. (3): Comparison between polycystic ovary syndrome (PCOS) and healthy women regarding the mean ± SD of serum glucose and Insulin Resistance.

Table 4: Analysis of Potential Factors Influencing Galanin Level Using Multiple Regression

Galanin	Coefficient of regression	p value
Cholesterol	-0.084	0.556
TG	0.348	<0.001
HDL	-0.457	<0.001
LDL	-0.113	0.433
VLDL	-0.112	0. 528
Insulin Resistance	0.474	<0.001

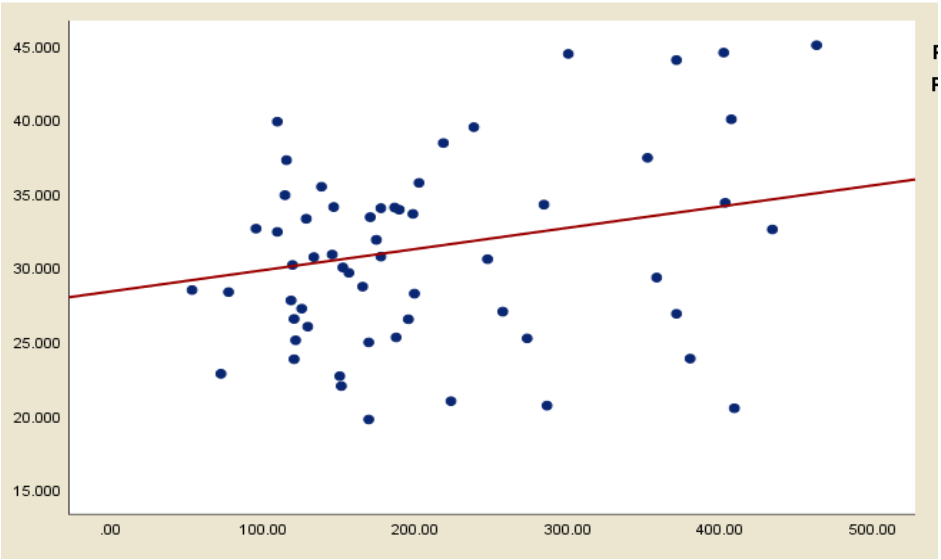

Fig. (4): Correlation between Galanin Level and HDL Level in Women with PCOs.

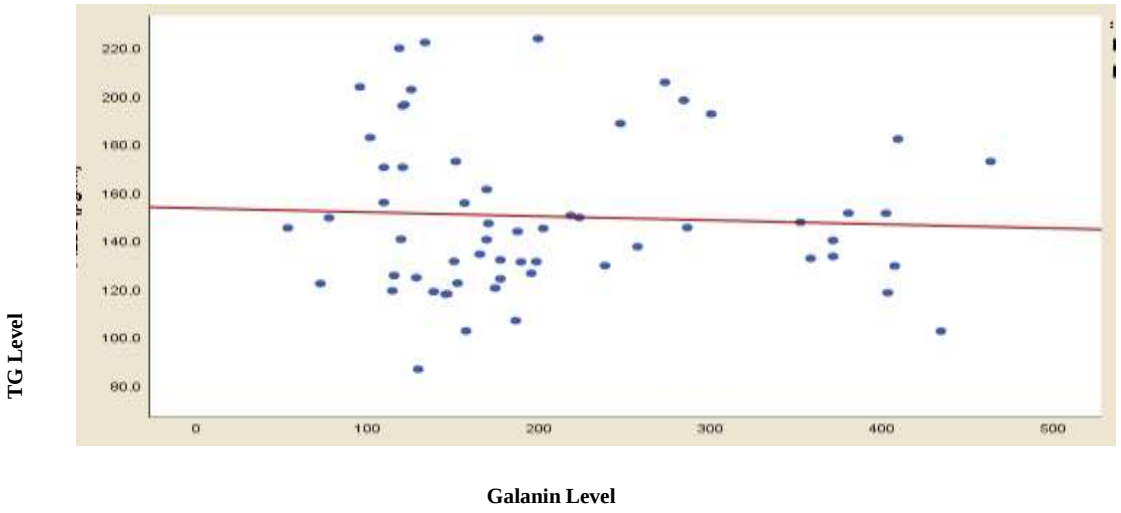

Fig. (5): Correlation between Galanin Level and TG Level in Women with PCOs.

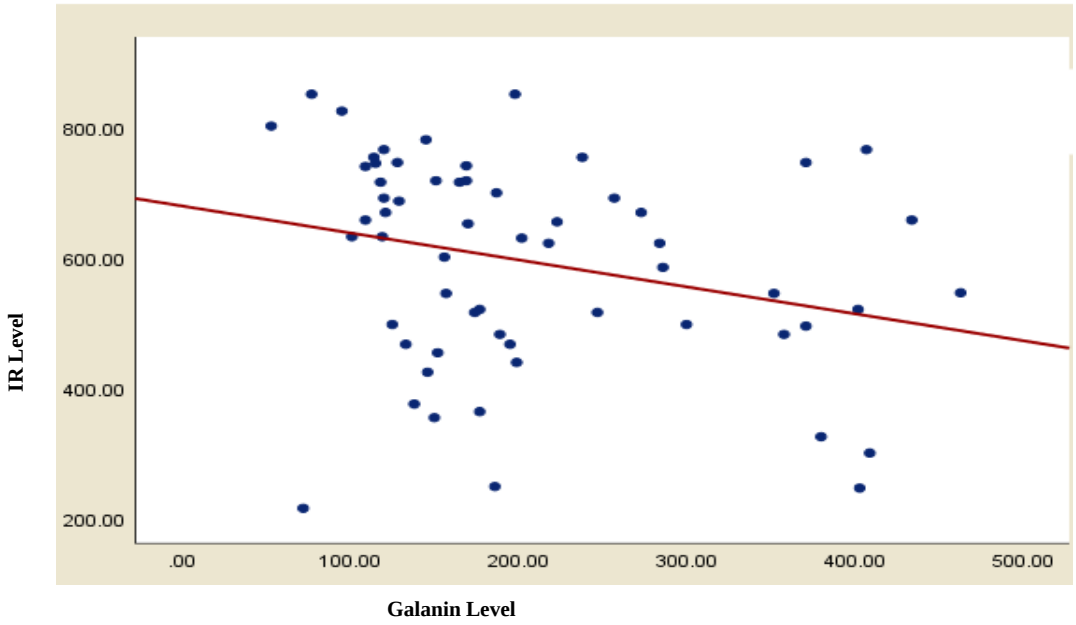

Fig. (6): Correlation between Galanin Level and IR Level in Women with PCOs.

4. DISCUSSION

Galanin affects insulin resistance, hypertension, metabolic syndrome, hunger, obesity, dyslipidemia, and reproduction. Many studies have connected galanin to polycystic ovarian syndrome (PCOS). This adipokine can be used as a marker for cardiovascular disease because it is more prevalent in polycystic ovarian syndrome (PCOS) (16).

In obese individuals, Acar et al. (17) found a favorable correlation between insulin resistance and triglycerides and galanin levels.Interestingly, exercise effectively increases the secretion of galanin. GLUT-4 translocation is positively impacted by exercise, and physical activity is necessary for the galanin system to lower insulin resistance , according to Fang et al. (18). A crucial phase in the development of polycystic ovarian syndrome (PCOS) is galanin resistance, which differentiates high levels of circulating galanin from poor glucose regulation in the diabetic population (19). On the other hand, obesity and galanin resistance are believed to be significantly correlated. However, nothing is known about galanin levels in PCOS patients. PCOS patients had greater levels of galanin than the control group, however this difference was not statistically significant, according to Baranowska et al. (20).

Similarly, PCOS patients with a BMI of >30 and those without a BMI of <30 had lower levels of galanin, according to Bidzińska-Speichert et al. (21). It was surprising to learn that PCOS patients had decreased circulating levels. Our results point to a link between insulin resistance and galanin deficiency in PCOS. Since galanin is a hormone that promotes insulin

sensitivity through GLUT-4 translocation, galanin deficiency may be one of the primary causes of insulin resistance in PCOS. Because galanin promotes insulin sensitivity by boosting GLUT-4 translocation and decreasing pancreatic insulin production, the results of the current investigation led us to conclude that a lack of galanin is associated with insulin resistance in the PCOS patient population [22].

Insulin can directly contact thecal cells and have a significant physiological impact because to special, highly-affinity insulin receptors found in the human follicular membrane. Insulin has the ability to directly stimulate the formation of androstenedione in thecal cells. Recent studies have linked deregulation of the mammalian target of rapamycin complex 1-autophagy pathway, which results in skeletal muscle insulin resistance triggered by hyperandrogenism, to mitochondrial damage and reduced glucose absorption (23). Therefore, people with PCOS who have insulin resistance and hyperinsulinemia may be more susceptible to hyperandrogenism in a number of ways (24). In addition to lowering the liver's production of SHBG (sex hormone binding globulin), which raises blood levels of free and bioactive androgens, hyperinsulinemia also results in metabolic and cardiovascular issues. improving the way ovarian cells react to luteinizing hormone (LH), which raises androgen production and is dependent on it. Hyperandrogenism exacerbates metabolic issues in women [25].

Blood sugar levels are normal when insulin resistance is present, but the pancreas releases more insulin when insulin levels are high. Weight gain and inflammation may result from using insulin excessively (26). The ovaries may produce more testosterone and prevent ovulation if there is too much insulin in the blood. Hyperinsulinemia also slows follicular maturation and development and stimulates LH receptors in theca cells, aggravating androgen-dependent anovulation [27].

Oxidative stress results from the production of reactive oxygen species by mononuclear cells due to hyperglycemia induced by insulin resistance. Oxidative stress, which also destroys cells and initiates the transcription of pro-inflammatory cytokines like tumor necrosis factor-alpha, is known to induce insulin resistance. This pro-inflammatory condition may also lead to hyperandrogenism and insulin resistance [28].

Additionally, we discovered high insulin levels, which in PCOS patients may indicate insulin resistance. The recent study indicates that women with PCOs have elevated insulin levels, which supports (29). Women with PCOS may develop hyperinsulinemia due to increased phosphorylation of insulin receptor proteins, which lowers protein tyrosine kinase activity and causes inappropriate insulin release. The insulin sensitivity of women with PCOS who are ovulatory and those who are anovulatory varies considerably. Insulin resistance is seen in anovulatory PCOS individuals, but not in women with a regular menstrual cycle who show symptoms of hyperandrogenism [30].

The poor reproductive outcomes of PCOS women are partly caused by insulin resistance and the resulting hyperinsulinemia. Reducing circulating insulin levels by various means has resulted in a decrease in androgen levels in women with PCOS. Even a 7% decrease in body weight has been shown to significantly reduce hyperandrogenism. Short-term use of drugs like somatostatin or diazoxide that lower insulin production has comparable outcomes. Metformin medication, which primarily inhibits hepatic gluconeogenesis, can lower testosterone levels in PCOS when paired with a reduction in blood insulin levels [31].

The results of Çatal and Kovalak (32) that shown a marked rise in LDL and cholesterol levels in PCOs with obese women are corroborated by the current investigation.

According to Swetha et al., a positive correlation between hyperglycemia and BMI and dyslipidemia in PCOS women may be supported by greater TC, TGs, LDL-cholesterol, and extremely LDL cholesterol in PCOS women compared to control (33).
VLDL and TG appear to increase in response to higher insulin levels. Additionally, this procedure can result in a rise in low-density and intermediate-density lipoproteins [34].

Weight had an impact on LDL and HDL levels in PCOS-afflicted women; those who were thinner had higher LDL and lower HDL than those who were obese. Despite being an issue for women with PCOS, they contend that dyslipidemia is not a sign of the disorder. In PCOS individuals with normal menstrual cycles, Glueck et al. investigated the association between cardiovascular risk factors, free testosterone, and obesity. According to their findings, PCOS patients have lower levels of HDL and higher levels of BMI, insulin, TGs, LDL, and free testosterone than the control group [35].

A linear regression analysis revealed that PCOS was primarily linked to lower HDL-C levels and higher TG levels, both in the general population and in PCOS phenotype 1, which was linked to the lower quartile of HDL-C levels. Similar findings were made by Gunning and Fauser (36) in a large cohort study. They found that women with PCOS had lower HDL-C concentrations and that PCOS was associated with higher levels of CHO, LDL-C, and TG.

According to a previous meta-analysis by Bizoń, women with PCOS are more likely to have cardiovascular illness in addition to having a higher BMI (37). Furthermore, we discovered that patients with PCOS phenotype 1 and the entire group of women with PCOS had a strong association between their TG (positive) and HDL-C (negative) levels. Additionally, there is a definite correlation with a decreased HDL-C level. Previous research on Chinese women with PCOS revealed similar findings, and they were substantially linked to lower HDLC levels regardless of IR or obesity [38].

The negative association between TG levels and concentrations in PCO women indicates a substantial link between those metabolic and hormonal indicators. Lipid problems were more prevalent in PCOS patients with hyperandrogenism and hyperinsulinemia levels, according to recent research by Zhu et al. (39). A strong association between variations in HDL-C and TG concentrations was found by our study's multiple regression analysis; further research is required to determine the mechanism behind these relationships. Additionally, only unbound testosterone was said to be active and capable of binding the androgen receptors in the target tissues of the body.

5. CONCLUSION

1-Serum Human GALP (Galanin-like peptide) levels in women with PCOS reduction compared with the control group. The findings indicate that the serum levels of prolactin, insulin resistance, and lipid profile were significantly elevated in women with PCOS.

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