Article

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Leptin Gene Polymorphism (–2548 G/A) and Its Relationship With Serum Leptin in Polycystic Ovary Syndrome

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Background: Polycystic ovary syndrome (PCOS) is a common hormone disorder in women of reproductive age. It is often associated with changes in adipokine signaling, obesity, and insulin resistance. The leptin gene produces a hormone that helps control energy balance and reproductive health. The –2548G>A promoter polymorphism in this gene might affect how leptin is expressed and metabolized, but findings have differed between populations. This study aims to investigate the distribution of –2548G>A genotypes and serum leptin levels in women with PCOS.

Methods: The study included 100 women with PCOS and 100 healthy controls of similar age, recruited between July 2023 and September 2025. Researchers measured physical, hormonal, and metabolic factors. They used enzyme-linked immunosorbent assay (ELISA) to check serum leptin levels and polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) to identify –2548G>A genotypes. Data analysis was done with SPSS version 25.0.

Results: There were no significant differences between the groups in age, body mass index, or other biochemical and hormonal measures ($p > 0.05$). However, the A/A genotype of the –2548G>A polymorphism was more common in the PCOS group than in controls ($p = 0.03$). There was no significant link between –2548G>A genotypes and blood leptin levels.

Conclusions: The –2548G>A polymorphism may raise the risk of developing PCOS, but it does not seem to affect blood leptin levels. Larger studies that include leptin receptor variants and functional tests are needed to better understand how leptin regulated in PCOS.

Keywords: leptin; polymorphism; polycystic ovary syndrome; leptin gene

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder that affects women of reproductive age around the world. Depending on which diagnostic criteria are used, its prevalence is estimated to be between 6% and 20% [1,2]. PCOS is marked by clinical or biochemical signs of high androgen levels, problems with ovulation, and polycystic ovaries. Although the exact cause is still unknown, PCOS is generally seen as a condition that results from a mix of genetic, hormonal, and environmental factors [3,4]. In addition to its effects on reproduction, PCOS is closely linked to metabolic problems like insulin resistance, obesity, abnormal cholesterol levels, and a higher risk of type 2 diabetes [3]. These metabolic issues play a major role in the development and long-term complications of PCOS. For this reason, understanding how metabolic problems and reproductive symptoms are connected is a key goal in PCOS research.

Leptin is one of the metabolic regulators that has drawn a lot of interest in PCOS research. It is a 16 kDa hormone produced by fat cells and is encoded by the *LEP* gene on chromosome 7q31.3 [5]. Leptin helps control energy balance by affecting appetite and how the body uses energy through pathways in the brain. Besides its role in metabolism, leptin also helps regulate reproduction by influencing hormone secretion, the development of ovarian follicles, and steroid production [6]. Problems with leptin signaling, including resistance to leptin, have been suggested as possible causes of ovulation problems and infertility in women with PCOS [7,8].

Even though there has been a lot of research, the link between leptin levels in the blood and PCOS is still debated. Some studies and meta-analyses have found that women with PCOS have higher leptin levels, especially when linked to body mass index (BMI) and insulin resistance [2,6,9,10]. However, other studies show that this link becomes weaker after accounting for body fat and other metabolic factors [11]. These mixed results show that leptin regulation is complex and depends on the situation. Differences in study design, the people studied, sample sizes, methods, and genetic factors may explain these inconsistencies.

Genetic factors are thought to play a big role in the differences seen in PCOS. Researchers have looked at changes in genes that control adipokines, especially the *LEP* gene, to see if they affect the risk of developing PCOS. One such change is the –2548G>A (rs7799039) variant, found in the promoter region of the *LEP* gene, which has been widely studied because it may affect how the gene works. This variant may change gene expression by affecting how certain proteins, like specificity protein 1 (Sp1), bind to DNA [12]. Studies looking at the link between the –2548G>A variant, leptin levels, obesity, and PCOS have found mixed results [13,14,15,16,17]. These differences highlight that leptin regulation is complex and affected by genetics, metabolism, hormones, and other factors.

Leptin signaling is controlled not just by the *LEP* gene, but also by the leptin receptor (LEPR) and other related pathways. Changes in the *LEPR* gene and other genes related to adipokines can affect how leptin works and may help explain the different symptoms seen in PCOS [18]. Because of this, the impact of a single genetic change may be small and depend on the situation. Genetic variants can also affect disease risk through ways that do not involve changes in hormone levels in the blood. These include interactions between genes, changes in gene regulation, and links with other important genetic sites.

Because the evidence is limited and inconsistent, especially in Turkish populations, more research is needed on the link between the *LEP –2548G>A* polymorphism and PCOS. This study set out to compare blood leptin levels in women with PCOS and healthy controls, and to look at how the *LEP –2548G>A* polymorphism relates to leptin levels and the risk of PCOS in a group of Turkish women. The mixed results from previous studies show that leptin regulation is complex and depends on both genetic and metabolic factors.

Methods

Study Design and Population

This case–control study received approval from the Clinical Research Ethics Committee of Çanakkale Onsekiz Mart University (Decision No: 2023/09-04) and followed the Declaration of Helsinki. All participants gave written informed consent before joining the study. The research took place from July 2023 to September 2025 at the Department of Obstetrics and Gynecology, Faculty of Medicine, together with the Health Services Vocational College at the same university. The study included 200 women: 100 patients with PCOS and 100 healthy controls matched by age. A specialist physician diagnosed PCOS using the Rotterdam criteria (2003), which require at least two of the following: oligo/anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology confirmed by ultrasonography [19].

Women in the control group had regular menstrual cycles (21 to 35 days), normal ovarian morphology, and no clinical or biochemical signs of hyperandrogenism. All participants were between 19 and 45 years old and had not received hormonal or metabolic treatment in the three months before samples were collected. The study excluded anyone who was pregnant or lactating, or who had a history of thyroid or adrenal disorders, diabetes mellitus, chronic inflammatory or autoimmune diseases, liver or kidney problems, or recent infections. Each participant gave a detailed medical and reproductive history and then had a full physical exam by an obstetrician–gynaecologist.

Sample Size and Power

We conducted a post hoc power analysis using G*Power software (version 3.1; Heinrich Heine University Düsseldorf, Düsseldorf, Germany). Based on the observed effect size derived from the analysis of variance (ANOVA) results for leptin levels across genotypes, with a significance level (α) of 0.05 and a total sample size of 200, the statistical power was calculated to be approximately 0.68.

Biochemical Analysis

Fasting venous blood samples were collected from all participants following an overnight fast of at least eight hours. Serum levels of glucose, insulin, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), vitamin D, and vitamin B_{12} were measured using an automated analyzer (Mindray BS-400, China). Insulin resistance was assessed using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), which is calculated based on fasting glucose and insulin levels as previously described [20]. All biochemical analyses were performed in duplicate, and samples were analyzed within the same batch to minimize inter-assay variability.

DNA Extraction and Genotyping of LEP –2548G>A (rs7799039)

Peripheral venous blood samples (approximately 3 mL) were collected in ethylenediaminetetraacetic acid (EDTA)-containing tubes and stored at –20 °C until analysis. Genomic DNA was extracted from peripheral leukocytes using a commercial DNA extraction kit (AccuPrep Genomic DNA Extraction Kit, Bioneer, Daejeon, South Korea; Catalog No: K-3032) according to the manufacturer's protocol. Genotyping of the LEP –2548G>A (rs7799039) polymorphism was performed using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method. PCR amplification was carried out in a total reaction volume of 25 µL containing genomic DNA, specific primers, dNTPs, $MgCl_2$, and Taq DNA polymerase (Thermo Fisher Scientific, Waltham, MA, USA; Catalog No: EP0402). The primer sequences

used were as follows: forward 5′-TTT CTG TAA TTT TCC CGT GAG-3′ and reverse 5′-AAA GCA AAG ACA GGC ATA AAA A-3′. The PCR products were digested with the HhaI restriction enzyme (New England Biolabs, Ipswich, MA, USA; Catalog No: R0139) at 37 °C overnight, following the manufacturer's instructions. The resulting fragments were separated using electrophoresis on a 3% agarose gel stained with ethidium bromide, then visualized under ultraviolet light. To check genotyping accuracy, 10% of the samples were randomly chosen and reanalyzed, and the results matched the initial findings exactly, as previously described [21].

Measurement of Serum Leptin Levels

We measured serum leptin concentrations with a commercial ELISA kit (Elabscience, Houston, TX, USA; Catalog No: E-EL-H0113) following the manufacturer's instructions. The analytical sensitivity of the assay was 0.2 ng/mL. Serum leptin concentrations obtained from the ELISA assay were converted from pg/mL to ng/mL for standardization with previously published studies and ease of comparison across the literatüre [22]. The intra- and inter-assay coefficients of variation were maintained below 5% and 8%, respectively, according to the manufacturer's assay protocol.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as frequencies and percentages. Data normality was assessed using the Shapiro–Wilk test, while homogeneity of variances was evaluated using Levene's test. Normally distributed variables are presented as mean ± standard deviation and compared using independent-samples t-tests, while non-normally distributed variables are expressed as median (interquartile range, IQR) and analyzed using the Mann–Whitney U test. Genotype distributions were compared using Fisher's exact test due to small expected cell counts. Logistic regression analysis was performed to assess PCOS risk. Differences in leptin levels among genotypes were analyzed using one-way ANOVA. Differences in genotype and allele frequencies between groups were analysed using the chi-squared (χ^2) test. Hardy–Weinberg equilibrium was assessed for genotype distributions in both groups. The association between LEP polymorphism and PCOS risk was evaluated using binary logistic regression analysis and the results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Differences in serum leptin levels among genotypes were analysed using one-way ANOVA with Bonferroni post hoc correction. A p-value of less than 0.05 was considered statistically significant.

Results

Clinical and Metabolic Characteristics of the Study Population

The demographic, anthropometric, and biochemical characteristics of the study population are summarized in Table 1. No significant differences were observed between the groups regarding age, BMI, glucose, insulin, HOMA-IR, TSH, FSH, total cholesterol, HDL-C, vitamin D, vitamin B12, or leptin levels (all $p > 0.05$). However LDL-C, and triglyceride levels differed significantly between the PCOS and control groups ($p < 0.05$). Collectively, these findings indicate that the two groups were metabolically and demographically comparable. Serum leptin concentrations were lower in women with PCOS compared to healthy controls (29.44 ± 16.12 vs. 32.72 ± 18.28 ng/mL), although this difference did not reach statistical significance ($p = 0.18$). Overall, these findings suggest that the two groups were similar in terms of their demographic and metabolic characteristics.

Distribution of LEP –2548G>A Genotypes and Association With PCOS Risk

The genotype and allele distributions of the *LEP –2548G>A* polymorphism are presented in Table 2. A significant difference in genotype distribution was observed between the PCOS and control groups ($p = 0.03$), primarily due to the higher frequency of the AA genotype among women with PCOS. However, allele frequencies did not differ significantly between groups. The genotype distributions in both groups were consistent with the Hardy–Weinberg equilibrium ($p > 0.05$).

To further investigate the relationship between *LEP* polymorphism and PCOS susceptibility, logistic regression analysis was performed using the GG genotype as the reference category (Table 3). Although the AG genotype was not significantly associated with PCOS risk, carriers of the AA genotype exhibited increased odds of PCOS.

Association Between LEP Genotypes and Circulating Leptin Levels

Serum leptin concentrations according to *LEP –2548G>A* genotypes are summarized in Table 4. No statistically significant differences in circulating leptin levels were observed among genotypes within the PCOS group ($p = 0.91$). Due to the limited number of AA genotype carriers in the control group, statistical comparisons were not considered reliable and were therefore presented descriptively.

Subgroup Analysis According to Insulin Resistance Status

To evaluate the potential influence of metabolic heterogeneity, PCOS patients were stratified according to insulin resistance status based on HOMA-IR values. As expected, insulin-resistant individuals demonstrated signifi-

Table 1. Socio-demographic and clinical characteristics of study groups.

Variables	PCOS (n = 100)	Controls (n = 100)	*p* value
Age (year)	25.76 ± 5.80	25.66 ± 5.25	0.90
BMI (kg/m^2)	26.15 ± 5.75	26.59 ± 3.69	0.51
Glucose (mg/dL)	90.48 ± 12.18	91.94 ± 15.06	0.45
Insulin (µIU/mL)	11.50 (9.20–18.73)	11.15 (9.20–19.80)	0.99
HOMA-IR (%)	2.60 (2.01–3.73)	2.24 (1.70–3.79)	0.51
TSH (µIU/mL)	2.16 ± 0.88	2.22 ± 0.84	0.61
FSH (mIU/mL)	5.64 ± 1.98	5.80 ± 2.06	0.57
TG (mg/dL)	110.55 (69.00–141.85)	122.00 (83.90–180.70)	0.04
TC (mg/dL)	182.84 ± 38.61	188.05 ± 39.17	0.34
LDL-C (mg/dL)	104.51 ± 35.68	115.53 ± 30.46	0.02
HDL-C (mg/dL)	61.65 ± 15.77	63.84 ± 17.23	0.34
Serum Vitamin D (ng/mL)	16.68 ± 6.52	17.27 ± 6.85	0.53
Serum Vitamin B12 (ng/mL)	336.12 ± 97.03	330.51 ± 108.60	0.67
Leptin (ng/mL)	29.44 ± 16.12	32.72 ± 18.28	0.18

Normally distributed variables are presented as mean ± SD and were compared using the independent-samples *t*-test. Insulin, HOMA-IR, and TG are presented as median (IQR) and were compared using the Mann–Whitney U test. BMI, Body Mass Index; TC, Total Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; TG, Triglycerides; HOMA-IR, Homeostatic Model Assessment; SD, Standard Deviation; PCOS, polycystic ovary syndrome; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone. Leptin values were converted to ng/mL for standardization with previously published literature.

Table 2. Genotype and allele frequencies of *LEP –2548G/A* polymorphism in PCOS and controls.

Genotype	PCOS (n = 100, %)	Controls (n = 100, %)	*p* value
GG	54 (54.0)	52 (52.0)	
AG	36 (36.0)	46 (46.0)	0.03
AA	10 (10.0)	2 (2.0)	
Allele frequencies			
G	144 (72.0)	150 (75.0)	0.49
A	56 (28.0)	50 (25.0)	

Data are presented as number of cases with frequency in parentheses. Genotype distributions were compared using Fisher's exact test due to low expected frequencies in some cells. LEP, leptin.

Table 3. Logistic regression analysis for association between *LEP –2548G>A* polymorphism and PCOS risk.

Genotype	OR	95% CI	*p* value
GG	1.00 (reference)	–	–
AG	0.75	0.41–1.37	0.35
AA	4.81	1.01–22.87	0.048

OR, odds ratio; CI, confidence interval.

cantly higher fasting insulin and HOMA-IR levels compared with non-insulin-resistant patients. However, serum leptin concentrations did not differ significantly between subgroups (Table 5).

Discussion

The present study investigated the association between the *LEP –2548G>A* (rs7799039) polymorphism and circulating leptin levels in Turkish women with PCOS. Our findings suggest that, although serum leptin concentrations were slightly lower in the PCOS group than in healthy controls, this difference was not statistically significant. Furthermore, while a significant difference in genotype distribution was observed—primarily due to a lower frequency of the AA genotype in the control group—no significant association was identified between *LEP* genotypes and serum leptin levels in either group.

In the present study, serum leptin concentrations were lower in women with PCOS compared to healthy controls; however, this difference did not reach statistical significance. It is important to consider that both groups had simi-

Table 4. Leptin levels in *LEP –2548G/A* genotypes of PCOS and Controls groups.

PCOS (n = 100, %)	Leptin (ng/mL)	*p* value
GG (54.0)	29.77 ± 16.39	
AG (36.0)	28.52 ± 16.32	0.91
AA (10.0)	30.93 ± 8.92	
Controls (n = 100, %)		
GG (52.0)	35.01 ± 21.49	
AG (46.0)	30.19 ± 19.19	
AA (2.0)	20.33 ± 2.57	

Data are expressed as means ± SD. Differences in leptin levels among genotypes were analyzed using one-way ANOVA followed by post-hoc tests where appropriate. Statistical comparison was performed only for the PCOS group due to insufficient sample size in the AA genotype subgroup of the control group (n = 2). Control group data are presented descriptively.

Table 5. Subgroup analysis based on insulin resistance (HOMA-IR ≥2.5) in PCOS patients.

Variables	IR (+) (n = 52)	IR (–) (n = 48)	*p* value
Age (years)	25.56 ± 6.72	25.98 ± 4.89	0.72
BMI (kg/m^2)	26.48 ± 6.59	25.79 ± 4.72	0.55
Glucose (mg/dL)	91.27 ± 14.72	89.63 ± 9.03	0.50
Insulin (µIU/mL)	25.94 ± 2.81	10.74 ± 1.31	<0.001
HOMA-IR	5.25 ± 0.55	1.75 ± 0.48	<0.001
Leptin (ng/mL)	31.11 ± 11.60	27.63 ± 11.10	0.28
Genotype (n,%)			
GG	32.0 (61.5)	22.0 (45.8)	
AG	16.0 (30.8)	20.0 (41.7)	0.28
AA	4.0 (7.7)	6.0 (12.5)	

Data are presented as mean ± standard deviation (SD). Group comparisons were performed using independent-samples *t*-tests. IR (+): insulin-resistant PCOS patients, defined as HOMA-IR ≥2.5; IR (–): non-insulin-resistant PCOS patients, defined as HOMA-IR <2.5.

lar BMI and metabolic profiles when interpreting this finding. Because leptin levels are closely linked to body fat, the lack of a significant difference may be due to the similar metabolic traits in the study population. To check how reliable this result is, we used logistic regression analysis. The AA genotype was more common in the PCOS group, but the regression model suggests caution because the confidence interval was wide and there were few AA carriers in the control group. Overall, these results suggest that the –2548G>A polymorphism might be linked to PCOS risk in terms of distribution, but its ability to predict PCOS on its own is limited in this group.

The finding that leptin levels do not differ significantly between PCOS patients and controls matches earlier studies that found similar leptin concentrations in both groups, especially when accounting for body fat [11]. While some studies report higher leptin levels in women with PCOS, especially those who are obese, this is not always the case. These mixed results show that PCOS can appear in different forms and underline the need to consider factors like BMI and insulin resistance. Bibliometric analyses also show that PCOS research uses a range of methods and is shaped by changing research trends, which may help explain why study results sometimes differ [23,24,25,26].

At first, the lack of a strong link between leptin levels and insulin resistance in this study might seem at odds with previous research showing a close connection between leptin, body fat, and metabolic problems. There are several reasons for this difference. Leptin levels are more closely tied to total body fat and how fat is distributed than to insulin resistance alone. In this study, participants had similar BMI values, and we did not have detailed body composition data, which may have made it harder to see differences in leptin levels related to body fat. Also, the group studied had similar metabolic profiles and a balanced range of insulin resistance, so there was less variation in metabolic measures. This lower variability can make it harder to find associations in cross-sectional studies. Recent research also suggests that leptin resistance, rather than just the amount of leptin in the blood, may be more important for metabolic problems. So, not finding a direct link between leptin levels and insulin resistance here does not necessarily go against earlier studies. Instead, it shows that leptin regulation in PCOS depends on the specific context. Overall, these results highlight the need to consider differences in study populations and individual traits when looking at leptin-related findings.

In our study group, we did not find significant differences in BMI or insulin resistance markers between groups, which suggests that the participants had similar metabolic profiles. This could help explain why there was no difference in circulating leptin levels, since leptin secretion is closely linked to body fat and metabolic health. Instead of focusing only on leptin levels, it may be more important to consider problems with leptin signaling and leptin resistance as key factors in PCOS, especially in people with obesity and high insulin levels [3,23,27]. One issue to consider is the metabolic profile of our participants. PCOS is a varied condition, and while insulin resistance is common, it is not present in all cases. Most people in our study had only mild to moderate metabolic issues, which might seem different from the original idea that leptin signaling is tied to insulin resistance. However, we chose this group on purpose for methodological reasons. By selecting participants with similar BMI and metabolic measures, we tried to reduce the effects of obesity and severe insulin resistance on leptin levels. Since leptin is strongly affected by body fat and metabolic status, this approach helped us better study the specific effect of the *LEP –2548G>A* polymorphism. Insulin resistance was present but spread evenly among participants, and subgroup analyses showed that leptin levels

were not significantly affected by insulin resistance status. These results suggest that the lack of association we found is probably not just due to the way we selected our group. Still, it is important to note that our findings may only apply to people with mild or moderate metabolic issues in PCOS. In more severe cases with higher insulin resistance or obesity, the link between leptin signaling and metabolic problems may be stronger. Future research should include groups that represent the full range of PCOS types.

Our results indicate that the *LEP –2548G>A* polymorphism does not have a major effect on circulating leptin levels in this population. This variant is found in the promoter region and may affect how transcription factors bind [12], but its impact seems to be modest and depends on the context [24]. Other studies have also found no significant link between this polymorphism and leptin levels or PCOS risk [21,24].

Other studies have found significant links between the –2548G>A polymorphism and leptin levels or metabolic traits. For example, Sabi et al. [12] found that the *–2548G>A LEP* polymorphism was linked to higher leptin and glucose levels in obese people. In contrast, Ben Ali et al. [13] reported that the –2548A allele was linked to lower leptin levels in obese women. These differences may be due to ethnic backgrounds, environmental factors, or differences in the study groups, especially regarding obesity.

Leptin signaling depends not only on the *LEP* gene but also on the leptin receptor (LEPR) and its downstream pathways. Variants in the *LEPR* gene can affect how sensitive the receptor is and how it signals inside cells, which can change leptin's effects regardless of its levels in the blood [18,27,28]. Erel et al. [26] found that certain leptin receptor gene variants may be linked to PCOS. This suggests that changes in the receptor itself could help cause the disease, even if serum leptin levels stay the same. These results support the idea that problems with leptin signaling, rather than just changes in leptin production, may be more important in PCOS.

The subgroup analysis based on insulin resistance offers valuable insight into how leptin is regulated in PCOS. While people with insulin resistance had higher insulin levels and HOMA-IR scores, their serum leptin levels were similar to those without insulin resistance. This suggests that, in a group with similar metabolic backgrounds, insulin resistance alone may not directly affect leptin levels. Instead, factors like body fat, genetics, and receptor mechanisms likely play a larger role in leptin regulation in PCOS. The cohort had a balanced distribution of insulin resistance (52% vs. 48%), which supports the idea that the lack of association between leptin levels and PCOS is not due to uneven metabolic groups. There was also no significant link between L*EP –2548G>A* genotypes and leptin levels, even after considering insulin resistance. This suggests that this genetic variation does not have a strong independent effect on leptin levels. Still, these results should be viewed with caution. Although the subgroups were balanced, there was a lot of variation in leptin measurements, which might have made it harder to see small differences. Larger studies with more detailed metabolic data are needed.

Leptin affects both the metabolic and reproductive systems. It helps control appetite and energy use, and also influences gonadotropin secretion and ovarian function [6,27]. In PCOS, problems with leptin signaling have been linked to issues with follicle development and ovulation [7,8,29]. However, our results show that these changes may not occur in every case and can depend on the metabolic characteristics of the group studied.

This study has some limitations. First, while the sample size is similar to other genetic studies, the statistical power was moderate at about 68%, which may have made it harder to detect small effects. Second, we only looked at one polymorphism in the *LEP* gene and did not include *LEPR* variants or other genes related to adipokines. Third, leptin was measured just once, so we did not consider changes due to circadian rhythms or the menstrual cycle. Finally, we did not assess detailed body composition, even though this could give a better picture of leptin dynamics than BMI alone.

Although this study has some limitations, it supports previous research showing that the *LEP –2548G>A* polymorphism has a small but independent effect on circulating leptin levels and the risk of polycystic ovary syndrome (PCOS). These results strengthen the view that PCOS is a complex disorder caused by the combined effects of genetic, metabolic, and hormonal factors.

Future research should use integrative methods that combine genetic, metabolic, and molecular data, and should include larger and more diverse groups of participants. Studying how different genes interact, such as *LEP* and *LEPR* polymorphisms, along with epigenetic changes, could help us better understand how leptin is involved in PCOS.

Conclusions

This study looked at the link between the *LEP –2548G>A* (rs7799039) polymorphism and leptin levels in Turkish women with PCOS. Although leptin levels were a bit lower in the PCOS group than in healthy controls, the difference was not significant. This means that changes in leptin levels are not always seen in similar PCOS groups. There was a notable difference in genotype distribution, mainly because the AA genotype was less common. Still, there was no connection between *LEP* genotypes and leptin levels. These findings suggest that the –2548G>A polymorphism may have only a small or indirect effect on PCOS risk and is unlikely to have a major impact on leptin secretion by itself.

These results should be viewed in light of the fact that our PCOS group had mild to moderate metabolic issues,

so they may not show how leptin works in more severe, insulin-resistant cases. Our findings add to the evidence that leptin regulation in PCOS is complex and involves genetic, metabolic, and hormonal factors. Changes in leptin signaling, possibly through its receptors or related pathways, may matter more than changes in the leptin gene itself. Clinically, this shows that single-gene polymorphisms are limited as markers for PCOS risk or metabolic problems. A broader approach that looks at several genetic factors, adipokine levels, and metabolic measures will likely give a better picture of the differences in the disease.

Abbreviations

BMI, Body mass index; ELISA, Enzyme-linked immunosorbent assay; FSH, Follicle-stimulating hormone; HDL-C, High-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL-C, Low-density lipoprotein cholesterol; LEPR, Leptin receptor gene; PCOS, Polycystic ovary syndrome; PCR–RFLP, Polymerase chain reaction–restriction fragment length polymorphism; SNP, Single nucleotide polymorphism; TC, Total cholesterol; TG, Triglycerides; TSH, Thyroid-stimulating hormone.

Availability of Data and Materials

The datasets generated or analyzed during the current study are not publicly available due to patient privacy and ethical restrictions but are available from the corresponding author on reasonable request.

Author Contributions

SC, ESP, IEP, BNS and FB designed the research study and wrote the first draft. SC, ESP, IEP and FB performed the research. SC, BNS and ESP analyzed the data. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by Çanakkale Onsekiz Mart University's Clinical Research Ethics Committee (Decision No: 2023/09-04, Date: June 21, 2023; Application No: 2023-73) and was carried out in compliance with the Declaration of Helsinki's ethical guidelines. Each participant gave written informed consent after being briefed on the study's objectives and procedures.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of Generative AI and AI-Assisted Technologies in Manuscript Preparation

The AI tools used for language editing were ChatGPT (OpenAI) and DeepL. These tools were used solely to improve the readability and grammar of the manuscript. No AI tools were used for data analysis, interpretation, or generation of scientific content. After their use, the authors thoroughly reviewed, verified, and revised all content to ensure its accuracy and originality.

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