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Elevated Nesfatin-1 and Altered Reproductive Hormones in Polycystic Ovary Syndrome: A Comparative Case-Control Study.

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ABSTRACT

Background and Aim: Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder affecting reproductive-age women, characterized by hyperandrogenism, ovarian dysfunction, and metabolic disturbances. Nesfatin-1, a neuropeptide involved in appetite regulation, has been proposed as a potential link between metabolic and reproductive dysfunction. This study aimed to investigate the relationship between serum Nesfatin-1 levels, hormonal changes, and anthropometric parameters in women with PCOS.

Methods: A cross-sectional, case-control design was employed, including 60 women diagnosed with PCOS based on the Rotterdam criteria and 30 age-matched healthy controls. Anthropometric measurements were recorded, and fasting blood samples were collected during the early follicular phase. Luteinizing hormone, follicle-stimulating hormone, estradiol, progesterone, testosterone, and Nesfatin-1 were quantified using validated immunoassays. Between-group differences were assessed via independent samples t-tests or Mann–Whitney U tests, and correlation analyses were conducted to explore potential associations.

Results: Participants with PCOS demonstrated significantly elevated body mass index, prolonged menstrual cycles, and higher levels of luteinizing hormone and testosterone compared with controls, alongside reduced follicle-stimulating hormone and estradiol. Serum Nesfatin-1 concentrations were markedly greater in the PCOS group compared to healthy participants (580.182 ± 133.691 vs. 266.232 ± 69.0825 pg/mL; $p<0.001$). Nesfatin-1 showed positive correlations with testosterone ($R=0.264$, $p=0.048$) and estradiol ($R=0.279$, $p=0.031$).

Conclusion: These findings underscore the role of Nesfatin-1 as a potential biomarker linking metabolic dysregulation and reproductive abnormalities in PCOS. The elevated Nesfatin-1 levels may reflect a compensatory neuroendocrine response to hyperandrogenemia and insulin resistance. Future longitudinal and mechanistic studies are necessary to elucidate Nesfatin-1's pathophysiological significance and evaluate its therapeutic implications in managing PCOS.

Keywords: *Polycystic Ovary Syndrome; Nesfatin-1; Hyperandrogenism; Metabolic Dysfunction; Reproductive Hormones; Biomarker..*

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder in women of reproductive age, marked by hyperandrogenism, ovarian dysfunction, and polycystic ovarian morphology [1]. Its clinical manifestations, including menstrual irregularities, hirsutism, and infertility, often coexist with metabolic abnormalities such as insulin resistance, obesity, and dyslipidemia [2]. The etiology of PCOS involves dysregulated signaling within the hypothalamic–pituitary–ovarian (HPO) axis and disturbances in numerous metabolic pathways [3]. Reproductive biomarkers,

including luteinizing hormone (LH), follicle-stimulating hormone (FSH), and sex steroids (testosterone and estradiol), are pivotal for understanding the pathophysiology of PCOS and are commonly dysregulated in affected individuals [4].

Recent attention has focused on the roles of appetite-regulating peptides in the pathogenesis of PCOS [5]. Nesfatin-1, a peptide derived from the nucleobindin-2 (NUCB2) gene, has been identified as an anorexigenic factor that modulates energy intake and may influence hypothalamic–pituitary–gonadal (HPG) axis activity [6]. The mechanistic underpinnings by which nesfatin-1 may contribute to the pathophysiology of PCOS extend beyond its well-recognized anorexigenic and energy-homeostatic roles [7]. In addition to its central effects on feeding behavior, nesfatin-1 is increasingly being recognized as an active modulator of the hypothalamic pituitary ovarian (HPO) axis [8]. Several studies indicate that nesfatin-1 is expressed in key brain regions such as the arcuate nucleus and paraventricular nucleus , where it co-localizes with gonadotropin-releasing hormone (GnRH) neurons [9-11]. Through this colocalization, nesfatin-1 is thought to influence GnRH synthesis and secretion, thereby indirectly modulating pituitary release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are essential for ovarian follicular development and steroidogenesis [12,13]

At the cellular level, nesfatin-1 is proposed to act via a G protein-coupled receptor (with GPCR12 emerging as a potential candidate) that, once activated, triggers intracellular cascades such as the extracellular signal-regulated kinase (ERK1/2) pathway and modulates intracellular calcium levels [14]. These signaling events are critical not only for the regulation of GnRH neuronal activity but also for direct effects on peripheral tissues. For example, in pancreatic beta-cells, nesfatin-1 has been shown to enhance glucose-stimulated insulin secretion by promoting calcium influx through voltage-dependent potassium (Kv) channels —a mechanism that may contribute to insulin resistance, a common metabolic abnormality in PCOS [10,15].

Furthermore, emerging evidence suggests that Nesfatin-1 directly influences ovarian function by increasing the expression of anti-apoptotic gene bcl-2, stimulating proliferation/differentiation markers, enhancing ovarian steroidogenesis, and promoting glucose uptake and metabolism in the ovary [16]. It appears that through autocrine and paracrine signaling, nesfatin-1 can alter the local microenvironment of the ovary potentially impacting both folliculogenesis and the synthesis of sex steroids such as estradiol and testosterone [16]. Such actions may provide a mechanistic link between the metabolic disturbances seen in PCOS and reproductive dysfunction [17]. Moreover, regulation of nesfatin-1 expression by sex steroids such as estradiol and progesterone further supports its role as a local modulator within reproductive tissues [18].

Several investigations propose that alterations in Nesfatin-1 expression may serve as a link between disordered metabolic status and reproductive dysfunction , studies examining Nesfatin-1 levels in PCOS have produced variable findings [19]. While Wang, Li, Sun, Song, Zhao and Hu [20] reported significantly higher Nesfatin-1 concentrations in women with PCOS, Wang, Ma, Luo, Wang and Han [21] found no pronounced disparity when compared to healthy controls. These discrepancies have been attributed to differences in study design, ethnic variation, methodological approaches, and the heterogeneity inherent in PCOS phenotypes.

Given these discrepancies and the potential relevance of Nesfatin-1 to both metabolic and ovarian function, further investigation is warranted to clarify its role as a biomarker and its mechanistic influence in PCOS. Therefore, the current study aimed to measure serum Nesfatin-1 levels in women with PCOS and compare them to healthy controls, while simultaneously examining correlations with reproductive hormones and clinical parameters. By assessing Nesfatin-1 alongside key reproductive biomarkers, this research seeks to offer insights into the interplay between neuroendocrine regulation and the pathophysiology of PCOS.

2. MATERIALS AND METHODS

Study Design and Ethical Considerations

This case-control study was carried out at Babel Teaching Hospital for Pediatrics and Gynecology, Imam Sadiq Teaching Hospital, and Iskandaria General Hospital from January 1, 2024, to June 30, 2024. Ethical approval was granted by the Institutional Review Board (Approval Number: 4162), and all participants provided written informed consent before their inclusion in the study. The research protocol was designed and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki [22].

Participant Recruitment and Selection

This study enrolled a total of 60 women diagnosed with polycystic ovary syndrome (PCOS) and 30 age-matched healthy controls. The diagnosis of PCOS was established according to the 2003 Rotterdam criteria, requiring the presence of at least two of the following: oligo- or anovulation, clinical or biochemical hyperandrogenism, or polycystic ovarian morphology on ultrasound [23]. Individuals with thyroid dysfunction, hyperprolactinemia, congenital adrenal hyperplasia, Cushing's syndrome, or other endocrine disorders were excluded. Healthy controls, free from endocrine or metabolic conditions, were selected from the same community or outpatient clinic. Participants were women aged 18–40 years with a body mass index (BMI) ranging from 18 to 40 kg/m², who had not used hormonal therapy for at least three months prior to study enrollment. Exclusion criteria encompassed pregnancy, lactation, severe systemic illnesses (e.g., cardiovascular disease, malignancy), autoimmune disorders, and recent use of insulin-sensitizing agents or corticosteroids.

Clinical Assessment and Anthropometry

Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (Seca 213, Hamburg, Germany), and body weight was recorded to the nearest 0.1 kg with a calibrated digital scale (Seca 799, Hamburg, Germany). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m²). Blood pressure was measured in the seated position using an automatic sphygmomanometer (Omron M6 Comfort, Omron Healthcare Co., Ltd., Kyoto, Japan), with three readings obtained at five-minute intervals; the mean of the final two measurements was recorded.

Sample Collection and Processing

After an overnight fast of at least 12 hours, venous blood samples (10 mL) were collected from all participants between 08:00 and 09:00 a.m. in the early follicular phase (days 2–5) of their menstrual cycle (or on a random day in those with oligomenorrhea/amenorrhea). Samples were drawn into serum separator tubes (BD Vacutainer SST II, BD Biosciences, Franklin Lakes, NJ, USA) and allowed to clot at room temperature for 30 minutes. The tubes were then centrifuged at 3000 × g for 10 minutes, and serum aliquots were stored at −80 °C until further analysis.

Biochemical Measurements

Serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), progesterone (P4), and total testosterone (T) were quantified using a fully automated electrochemiluminescence immunoassay (ECLIA) on the Cobas e 601 analyzer (Roche Diagnostics, Mannheim, Germany). The intra-assay and inter-assay coefficients of variation (CV) for these assays ranged between 2% and 6%, and manufacturer-provided quality controls were run daily to ensure assay performance.

Nesfatin-1 Measurement

Serum Nesfatin-1 concentrations were determined via enzyme-linked immunosorbent assay (ELISA) using a commercially available kit (Elabscience, USA ; Cat. no. EL-H2373) with a lower detection limit of 15.0 pg/mL. Briefly, 50 µL of each standard or sample was added to the appropriate microplate well pre-coated with specific anti-Nesfatin-1 antibodies. After incubation at 37 °C for 90 minutes, plates were washed five times using the buffer supplied by the manufacturer. An HRP-conjugated secondary antibody (50 µL) was then added, and incubation proceeded for 30 minutes at 37 °C. Following another series of washes, 90 µL of TMB substrate solution was applied for color development over 15 minutes in the dark. The reaction was stopped by adding 50 µL of stop solution, and optical densities were measured at 450 nm using a microplate reader (BioTek ELx808, BioTek Instruments, Winooski, VT, USA). Sample concentrations were calculated from the standard curve generated by four-parameter logistic (4-PL) regression, and duplicate measurements were performed for all specimens to ensure reproducibility. The intra-assay and inter-assay CVs were <8% and <10%, respectively, per the manufacturer's specifications.

Statistical Analysis

Statistical analyses were conducted using SPSS version 28 (IBM Corp., Armonk, NY, USA) or an equivalent statistical software package. Continuous variables were summarized as mean ± standard deviation (SD), while categorical variables were reported as frequencies and percentages. The normality of data distribution was assessed using the Shapiro–Wilk test. For comparisons between groups, the unpaired t-test was applied to normally distributed variables, whereas the Mann–Whitney U test was used for non-normally distributed data. Categorical variables were analyzed using the chi-square test (χ^2). Correlations between epiregulin levels and various hormonal or metabolic parameters were examined using Pearson's correlation coefficient for normally distributed data and Spearman's correlation coefficient for non-normally distributed data. A p-value of less than 0.05 was considered indicative of statistical significance[24].

3. RESULTS

In **Table 1**, the control group (n=30) had a mean age of 29.13 ± 5.26 years, while the PCOS group (n=60) had a mean age of 30.63 ± 4.61 years (p=0.23, NS). BMI was significantly higher in the PCOS group (32.64 ± 6.73 kg/m²) compared to controls (26.76 ± 4.50 kg/m²) (p<0.001). The PCOS group also had a markedly longer cycle length (42.3 ± 4.42 vs. 27.76 ± 2.32 days; p<0.001) as well as elevated systolic (124.5 ± 9.25 vs. 120 ± 7.98 mmHg; p<0.001) and diastolic blood pressures (80.74 ± 4.85 vs. 74.66 ± 4.1 mmHg; p<0.001).

Table 1. Comparison of Baseline Demographic and Clinical Characteristics Between Control and PCOS Groups[a]

Characteristic	Control *n* = 30	PCOS *n* = 60	*P.value*
Age (years)			
Mean ±SD	29.13 ± 5.26	30.63 ± 4.61	0.23 I NS
BMI (kg/m²)			
Mean ±SD	26.76±4.502	32.64±6.73	<0.001 I***
Cycle Length (days)			
Mean ±SD	27.76 ± 2.32	42.3 ± 4.42	<0.001 I***
Systolic (mmHg)			
Mean ±SD	120 ± 7.98	124.5 ± 9.25	<0.001 I***
Diastolic (mmHg)			
Mean ±SD	74.66 ± 4.1	80.74 ± 4.85	<0.001 I***

a n: number of cases; SD: standard deviation; a Statistical significance was indicated by ***p<0.001. I: independent samples t-test. NS: Not Significant

In **Table 2**, women with PCOS (n=60) showed significantly elevated LH (0.871 ± 0.116 vs. 0.244 ± 0.160 µIU/mL) and testosterone levels (0.728 ± 0.091 vs. 0.424 ± 0.108 ng/mL), but markedly lower FSH (3.176 ± 0.643 vs. 5.428 ± 1.148 µIU/mL), estradiol (15.254 ± 2.185 vs. 88.452 ± 14.164 pg/mL), and progesterone (0.065 ± 0.082 vs. 0.317 ± 0.055 ng/mL) compared to controls (n=30), with all differences reaching p<0.001.

Table2. Comparison of Key Reproductive Hormone Levels Between Control and PCOS Groups[a]

Characteristic	Control *n* =30	PCOS *n* = 60	*p*
LH (µIU/ml)			
Mean ±SD	0.244 ±0.160	0.871±0.116	<0.001 I***
FSH (µIU/ml)			
Mean ±SD	5.428±1.148	3.176±0.643	<0.001 I***
Testosterone (ng/ml)			
Mean ±SD	0.424±0.108	0.728±0.091	<0.001 I***
Estradiol(pg/ml)			
Mean ±SD	88.452± 14.164	15.254±2.185	<0.001 I***
Progestrone(ng/ml)			
Mean ±SD	0.317±0.055	0.065±0.082	<0.001 I***

[a] n: number of cases; SD: standard deviation; a Statistical significance was indicated by ***p<0.001. I: independent samples t-test.

In **Table 3**, the PCOS group (n=60) showed a markedly higher mean serum Nesfatin-1 level (580.182 ± 133.691 pg/mL) compared to the control group (266.232 ± 69.0825 pg/mL), and this difference was highly significant (p<0.001).

Table 3. Serum Nesfatin-1 Levels in Control vs. PCOS Groups[a]

Characteristic	Control *n* =30	PCOS *n* = 60	p
Nesfatin-1(pg/ml) **Mean ±SD**	**266.23 ± 69.08**	**580.18 ± 133.69**	<0.001 I***

[a] n: number of cases; SD: standard deviation; a Statistical significance was indicated by ***p<0.001. I: independent samples t-test.

Figure 1 demonstrates a positive but modest correlation (R=0.264, p=0.048) between Nesfatin-1 and testosterone levels in women with PCOS, indicating that higher testosterone levels are associated with increased Nesfatin-1.

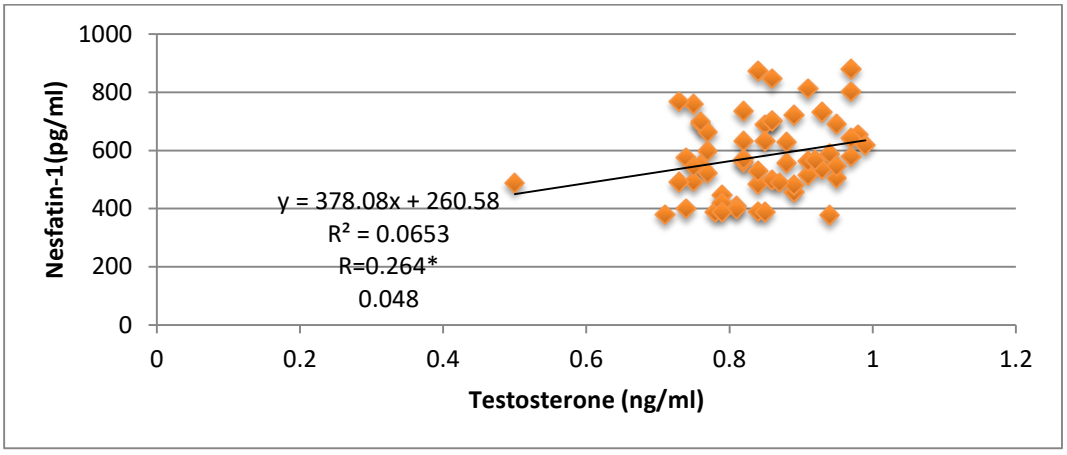

Fig.1 Correlation relationship between between Nesfatin-1(pg/ml) and Testosterone(ng/ml).

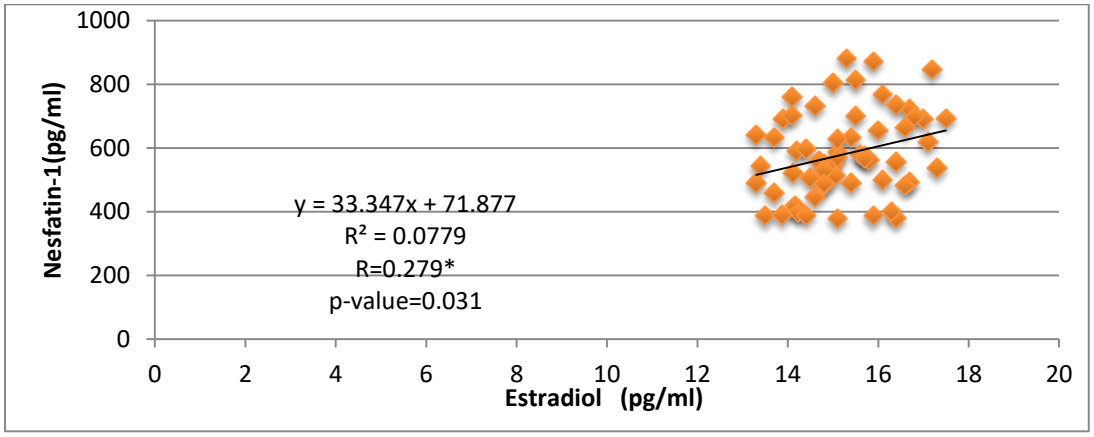

Fig.2 Correlation relationship betweenNesfatin-1(pg/ml) and Estradiol(pg/ml)

4. DISCUSSION

In this study, we conducted a thorough comparison of anthropometric indices, reproductive hormone levels, and circulating Nesfatin-1 concentrations between women with PCOS and healthy controls. Our findings revealed that individuals with PCOS had notably higher BMIs, longer menstrual cycles, and altered gonadotropin levels characterized by elevated LH and diminished FSH. In line with the classical hyperandrogenic signature, the PCOS patients also exhibited increased testosterone. Of particular importance, our investigation demonstrated significantly elevated Nesfatin-1 levels in PCOS, with positive correlations observed between Nesfatin-1 and both testosterone and estradiol. These results highlight the potential involvement of Nesfatin-1 in both the metabolic and reproductive disturbances characteristic of PCOS.

Our demonstration of higher Nesfatin-1 concentrations in PCOS aligns with the findings of Ademoglu, Gorar, Carlıoglu, Yazıcı, Dellal, Berberoglu, Akdeniz, Uysal and Karakurt [25] , who reported mean Nesfatin-1 levels of approximately 371.43 ± 2.50 pg/mL and also with Faeza, Pikee and Anju [7] that reported significant difference in serum Nesfatin 1 levels between PCOS subjects (8.6 ng/ml) and controls (0.75 ng/ml, $p<0.01$), in PCOS groups. By contrast, Wang, Ma, Luo, Wang and Han [21] did not observe a statistically significant difference in Nesfatin-1 between PCOS and control populations , suggesting that discrepancies may stem from variations in diagnostic criteria, sample size, ethnic background, menstrual phase during sample collection, or the diverse phenotypic presentations of PCOS.

Nesfatin-1 is a cleavage product of the nucleobindin-2 (NUCB2) gene, widely recognized for its appetite-regulating functions in the hypothalamus [6]. Beyond central energy homeostasis, emerging evidence indicates that Nesfatin-1 can modulate the hypothalamic-pituitary-gonadal (HPG) axis by influencing the release of gonadotropin-releasing hormone (GnRH) [8]. In PCOS, this modulation may be especially pertinent, as GnRH pulsatility is frequently altered, resulting in preferential LH secretion and subsequent hyperandrogenemia.

Furthermore, Nesfatin-1 may be involved in peripheral metabolism where chronic hyperinsulinemia, a hallmark of insulin resistance in PCOS, may upregulate NUCB2/Nesfatin-1 gene expression both centrally and in peripheral tissues [26]. Additionally, low-grade inflammation—commonly observed in PCOS can stimulate inflammatory mediators that enhance Nesfatin-1 release [6,27]. Hyperandrogenemia itself might create a feedback loop: elevated androgens can disrupt normal metabolic signaling in adipose tissue and the liver, leading to compensatory increases in appetite-regulating and insulin-sensitizing peptides, including Nesfatin-1[28,29]

Another possible mechanism relates to the interaction between Nesfatin-1 and other metabolic hormones such as leptin and ghrelin. Weibert, Hofmann, Elbelt, Rose and Stengel [30] reported that Nesfatin-1 may share downstream signaling pathways with leptin, another crucial regulator of appetite and energy expenditure. Since leptin levels are often dysregulated in obesity (a condition frequently comorbid with PCOS) [31] , elevated Nesfatin-1 may represent a compensatory response to counteract hyperphagia or metabolic imbalance. Additionally, Nesfatin-1 can influence glucose homeostasis by enhancing insulin secretion from pancreatic beta cells [10,15] ; thus, its elevation in PCOS could be linked to a compensatory drive to improve glycemic control in an insulin-resistant state. Overall, these interconnected pathways underscore a dual role for Nesfatin-1 in modulating both metabolic and reproductive physiology, potentially amplifying the pathophysiologic loops inherent in PCOS.

From a clinical perspective, our findings suggest that Nesfatin-1 measurement may offer added insight into the degree of metabolic and hormonal dysregulation in PCOS. In particular, the positive relationships between Nesfatin-1 and testosterone/estradiol imply that elevated Nesfatin-1 could be a surrogate marker for heightened androgenic and estrogenic activity, providing a more nuanced view of disease severity. If future research substantiates that Nesfatin-1 levels improve or normalize with interventions such as weight reduction, insulin-sensitizing medications (e.g., metformin), or anti-androgen therapy, clinicians might consider Nesfatin-1 as a complementary biomarker to track treatment efficacy or disease progression. On a therapeutic front, targeted modulation of Nesfatin-1 or its upstream regulators might represent a novel intervention strategy to correct both metabolic and reproductive abnormalities in PCOS.

A key strength of this study is the well-defined diagnostic criteria for PCOS, ensuring the enrollment of a relatively homogenous patient group. Additionally, we used standardized, validated assays to measure reproductive hormones and Nesfatin-1, enhancing the reliability and reproducibility of our results. The inclusion of correlation analyses between Nesfatin-1 and sex steroids further augments the mechanistic relevance of our findings, positioning Nesfatin-1 at the nexus of metabolic and endocrine disturbances in PCOS.

Nonetheless, the present investigation has several limitations. First, the cross-sectional design restricts our capacity to infer causal relationships—whether elevated Nesfatin-1 triggers or simply reflects the metabolic and hormonal imbalances in PCOS remains unclear. Second, our sample size, while adequately powered for detecting group differences, may not capture the full phenotypic diversity of PCOS. Third, unmeasured confounders such as dietary habits, physical activity levels, and psychological stress could influence Nesfatin-1 and hormone levels. Finally, although we attempted to standardize the timing of blood sampling, fluctuations during different phases of the menstrual cycle may still affect hormone and Nesfatin-1 measurements.

5. CONCLUSION

The present findings highlight the heightened Nesfatin-1 concentrations in women with PCOS and their significant associations with androgenic and estrogenic imbalances. This interplay underscores Nesfatin-1's potential role as a biomarker bridging metabolic and reproductive dysfunctions. By delineating these neuroendocrine interactions, our results contribute valuable insight into the multifactorial nature of PCOS. Nonetheless, longitudinal and mechanistic investigations are warranted to establish causal links and potential therapeutic implications. Such work may ultimately refine diagnostic precision and enhance management strategies for PCOS.

Conflict of Interest: We declare that there are no conflicts of interest associated with this manuscript.

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Authors contribution:

ZG (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing)

HA (Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing)

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