Metabolic and Inflammatory Adipokine Profiles in PCOS: A Focus on Insulin Resistance and Atherogenic Risk

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Article

Metabolic and Inflammatory Adipokine Profiles in PCOS: A Focus on Insulin Resistance and Atherogenic Risk

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Abstract

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder commonly linked to insulin resistance (IR); low-grade chronic inflammation; dyslipidemia; and altered adipokine secretion. This study aimed to assess serum concentrations of key adipokines—leptin; adiponectin; visfatin; and resistin—in women with PCOS; stratified by IR status; and to examine their relationship with anthropometric; metabolic; inflammatory; and atherogenic parameters. A total of 150 women diagnosed with PCOS were divided into two subgroups: with IR (n = 76) and without IR (n = 74). Serum adipokines were measured using ELISA; and atherogenic indices (TG/HDL-C; LDL-C/HDL-C; and AIP) were calculated from fasting lipid profiles. Anthropometric data included body weight; BMI; waist and hip circumferences; and waist-to-hip ratio. IR was evaluated using HOMA-IR; QUICKI; and the Matsuda index. Women with IR had significantly higher leptin; visfatin; and resistin levels; and lower adiponectin. Leptin correlated positively with HOMA-IR; body weight; and lipid ratios; while adiponectin showed inverse links to triglycerides; TG/HDL-C; and AIP. Resistin was positively related to IR indices; and visfatin showed a negative correlation with HDL-C and insulin sensitivity. These findings suggest that IR in PCOS is associated with a proinflammatory and atherogenic adipokine profile; potentially increasing cardiometabolic risk and guiding treatment approaches.

Keywords: polycystic ovary syndrome; insulin resistance; adipokines; atherogenic indices; metabolic dysfunction; inflammation

1. Introduction

Polycystic ovary syndrome (PCOS) is a multifactorial endocrine disorder affecting approximately 10–15% of women at reproductive age, depending on the applied diagnostic criteria, and represents one of the most common ovarian pathologies worldwide [1]. It is classically defined by the presence of oligo- or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology [2]. While historically regarded as a reproductive disorder, PCOS is now recognized as a complex metabolic condition, characterized by insulin resistance (IR), dyslipidemia, central obesity, and chronic low-grade inflammation [3–5].

Insulin resistance occurs in up to 70% of women with PCOS, independent of body mass index (BMI), and plays a pivotal role in the development of both reproductive and metabolic abnormalities [6]. IR contributes to compensatory hyperinsulinemia, which stimulates ovarian androgen production, disrupts folliculogenesis, and alters adipose tissue signaling [7]. Dysfunctional adipose tissue, through altered secretion of adipokines—bioactive cytokines produced by adipocytes—has

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emerged as a key component of this metabolic–inflammatory axis, influencing insulin sensitivity, lipid metabolism, and immune responses [8,9].

Among adipokines, leptin, adiponectin, visfatin, and resistin have been most extensively studied due to their distinct insulin-sensitizing or pro-inflammatory actions. Leptin and resistin levels are generally elevated in insulin-resistant states and show positive correlations with adiposity, pro-inflammatory cytokines, and cardiometabolic risk markers [10,11]. Adiponectin, an insulin-sensitizing and anti-inflammatory adipokine, is typically reduced in PCOS and inversely related to IR and dyslipidemia [12,13]. Visfatin has been reported to exert both insulin-mimetic and pro-inflammatory effects, although findings remain inconsistent [14]. Alterations in adipokine profiles may not only reflect underlying metabolic dysfunction but also contribute to systemic inflammation and reproductive impairment in PCOS [15].

Beyond IR, PCOS is frequently associated with atherogenic dyslipidemia, characterized by elevated triglycerides (TG), reduced high-density lipoprotein cholesterol (HDL-C), increased small dense low-density lipoprotein (sdLDL) particles, and unfavorable lipid ratios such as TG/HDL-C and LDL-C/HDL-C [16,17]. These alterations can be summarized by composite indices such as the Atherogenic Index of Plasma (AIP), a sensitive marker of cardiovascular risk [18]. Evidence suggests that certain adipokines may directly influence lipid metabolism, thereby linking adipose tissue dysfunction to atherogenesis [19].

However, few studies have simultaneously examined adipokines, IR, and lipid-related atherogenic markers in PCOS populations. Moreover, the extent to which insulin resistance drives adipokine–lipid associations, independently of obesity or androgen excess, remains unclear.

Therefore, the aim of this study was to compare serum concentrations of leptin, adiponectin, visfatin, and resistin in women with PCOS stratified by insulin resistance status, and to explore their relationships with anthropometric, metabolic, inflammatory, and atherogenic parameters. Elucidating these interactions may help clarify mechanisms underlying cardiometabolic risk in PCOS and identify potential targets for individualized metabolic intervention.

2. Results

2.1. Age and Anthropometric Parameters

Table 1 summarizes the age and anthropometric parameters of insulin-resistant (IR) and non–insulin-resistant (non-IR) women with PCOS. Both groups were similar in age and height. Compared to non-IR women, those with IR had significantly higher body weight, BMI, waist circumference, and hip circumference ($p < 0.01$). Waist-to-hip ratio (WHR) did not differ significantly.

Table 1. Age and anthropometric parameters in the two studied groups of PCOS women.

Parameters	Non-IR PCOS (n=74)	IR PCOS (n=76)
Age (years)	24.60 ± 4.53	24.03 ± 5.86 NS
Height (m)	1.67 ± 0.08	1.66 ± 0.05 NS
Weight (kg)	67.92 ± 15.94	78.08 ± 16.00 **
BMI (kg/m^2)	24.31 ± 5.28	28.40 ± 5.56 **
Waist (cm)	79.16 ± 13.45	89.21 ± 16.17 **
Hip (cm)	99.49 ± 10.75	107.82 ± 10.68 **
WHR	0.79 ± 0.08	0.82 ± 0.10 NS

NS – not significant, ($p > 0.05$); ** – $p < 0.01$.

2.2. Glucose and Insulin Dynamics

The oral glucose tolerance test (OGTT) revealed significantly elevated fasting, 60′, and 120′ glucose and insulin levels in the IR group compared to non-IR women ($p < 0.001$) (Figures 1 and 2).

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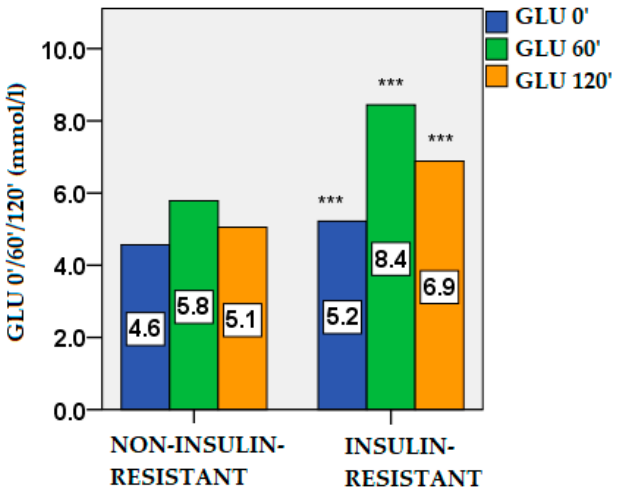

Figure 1. Glucose levels at baseline and during OGTT in IR and non–IR women with PCOS. *** – $p < 0.001$.

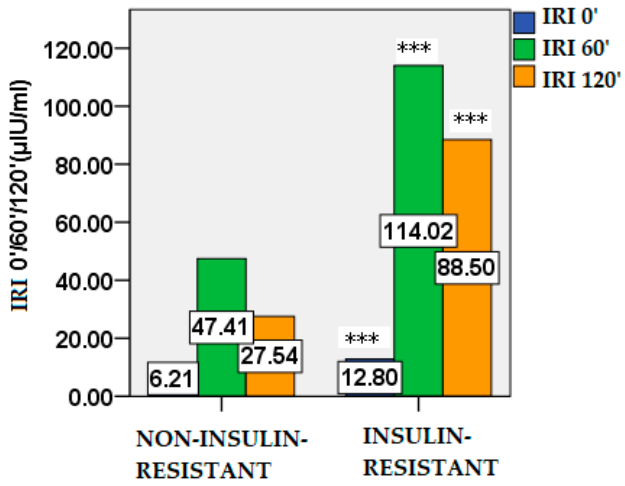

Figure 2. Insulin levels at baseline and during OGTT in IR and non–IR PCOS women. *** – $p < 0.001$.

In the IR cohort, HOMA-IR was significantly elevated (3.11 ± 1.77 vs. 1.28 ± 0.48; p < 0.001), accompanied by a reduction in QUICKI (0.33 ± 0.03 vs. 0.38 ± 0.03; p < 0.001) and a markedly lower Matsuda index (3.97 ± 1.73 vs. 11.77 ± 5.55; p < 0.001) (Figures 3–5). These findings confirm the validity of the insulin resistance classification applied in this study.

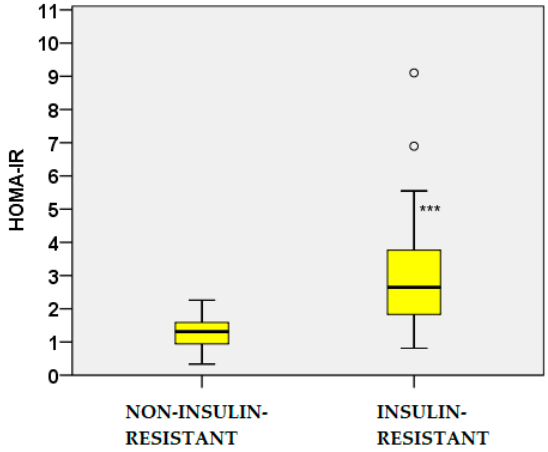

Figure 3. HOMA-IR values in IR and non–IR women with PCOS. *** – $p < 0.001$.

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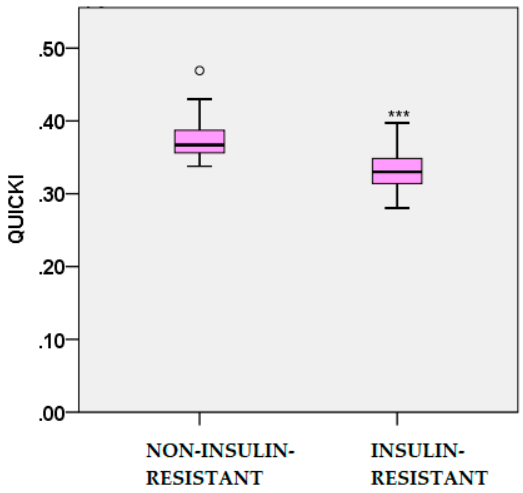

Figure 4. QUICKI values in IR and non–IR women with PCOS. *** – $p < 0.001$.

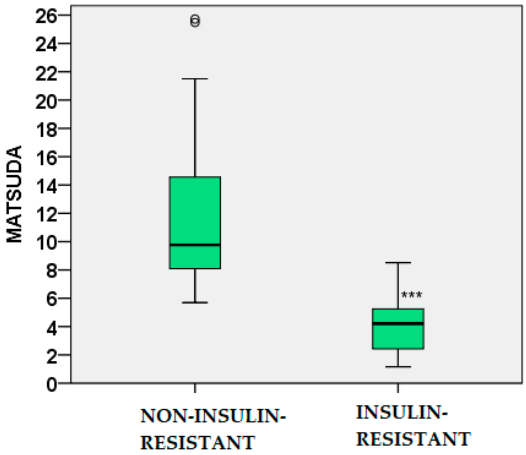

Figure 5. MATSUDA index values in IR and non–IR women with PCOS. *** – $p < 0.001$.

2.3. Lipid Profile and Atherogenic Indices

Table 2 presents lipid parameters and atherogenic indices in both groups. Compared to non-IR women, the IR group demonstrated significantly higher values of triglycerides (TG) ($p < 0.001$), TG/HDL-C ratio ($p < 0.01$), and Atherogenic Index of Plasma (AIP) ($p < 0.001$). No significant differences concerning total cholesterol (TC), HDL-C, LDL-C, or LDL-C/HDL-C ratios were observed (Table 2).

Table 2. Lipid profile parameters and calculated atherogenic indices in the two studied groups of PCOS women.

Parameters	Non-IR PCOS (n=74)	IR PCOS (n=76)
TC (mmol/l)	4.48 ± 0.93	4.46 ± 0.86 NS
HDL-C (mmol/l)	1.37 ± 0.49	1.23 ± 0.28 NS
LDL-C (mmol/l)	2.78 ± 0.92	2.67 ± 0.84 NS
TG (mmol/l)	0.80 ± 0.30	1.22 ± 0.60 ***
AIP	-0.09 ± 0.14	0.03 ± 0.19 ***
LDL-C/HDL-C	2.23 ± 0.92	2.32 ± 0.92 NS
TG/HDL-C	0.67 ± 0.34	1.06 ± 0.60 **

NS – not significant, ($p > 0.05$); ** – $p < 0.01$; *** – $p < 0.001$.

2.4. Adipokine Profiles

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Adipokine profiles differed significantly between groups (Table 3). Compared with non-IR women, those with IR exhibited higher visfatin ($p < 0.05$), leptin ($p < 0.01$), log_{10}-transformed resistin ($p < 0.05$) values, and lower adiponectin levels ($p < 0.01$).

Table 3. Adipokines in the two studied groups of PCOS women.

Adipokines	Non-IR PCOS (n=74)	IR PCOS (n=76)
Visfatin (ng/ml)	7.23 ± 3.76	14.05 ± 11.03 *
Leptin (ng/ml)	24.90 ± 18.37	39.56 ± 18.54**
Adiponectin (mcg/ml)	14.70 ± 7.74	9.19 ± 4.53 **
Log10 Resistin (ng/ml)	0.67 ± 0.20	0.81 ± 0.23 *

* – $p < 0.05$; ** – $p < 0.01$.

2.5. Correlation Analyses

2.5.1. Leptin

Serum leptin levels showed significant positive correlations with several anthropometric and metabolic parameters. Specifically, leptin was found to be strongly associated with body weight ($r = 0.732$, $p < 0.001$; Figure 6), BMI ($r = 0.694$, $p < 0.001$), and waist circumference ($r = 0.679$, $p < 0.001$). Moreover, a significant moderate positive correlation between the adipokine and HOMA-IR was observed ($r = 0.409$, $p < 0.001$; Figure 7), indicating a potential link between circulating leptin concentrations, adiposity, and insulin resistance.

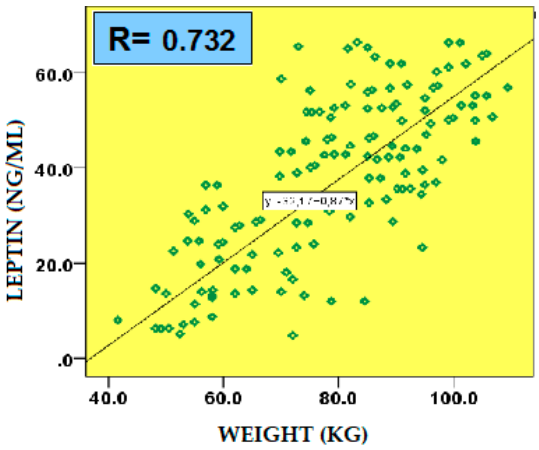

Figure 6. Scatter plot showing the positive correlation between leptin levels and body weight in the study population.

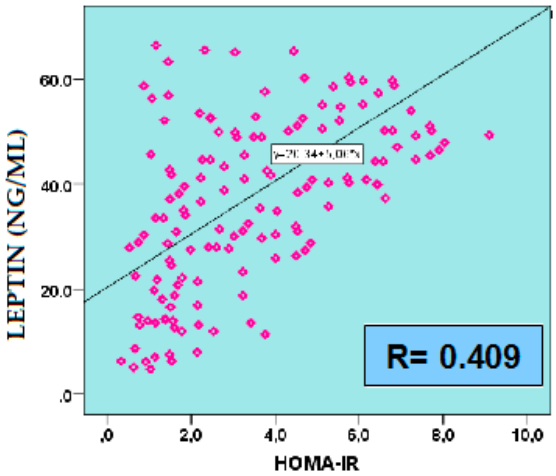

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Figure 7. Scatter plot showing the positive correlation between leptin levels and HOMA-IR in the study population.

In addition, leptin showed a negative correlation with both QUICKI ($r = –0.430$, $p < 0.001$; Figure 8) and Matsuda index ($r = –0.423$, $p < 0.001$; Figure 9).

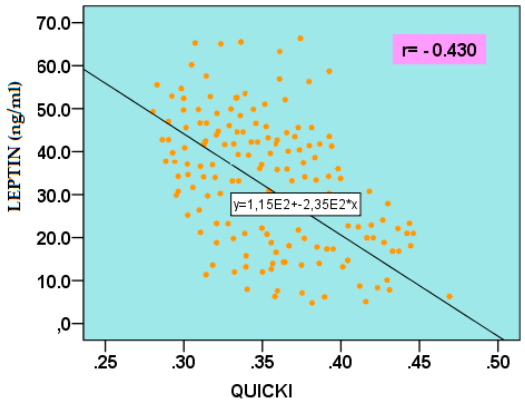

Figure 8. Scatter plot showing the negative correlation between leptin levels and QUICKI in the study population.

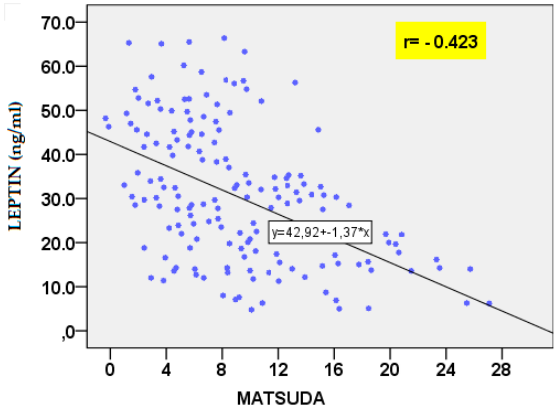

Figure 9. Scatter plot showing the negative correlation between leptin levels and MATSUDA in the study population.

Using linear regression analysis, it was found that weight explains 54% of the variations in leptin levels ($R = 0.732$, $R^2 = 0.536$, $P < 0.001$, $F = 73.96$). Thus, an increase in weight by 1 kg leads to an increase in leptin levels by 0.87 ng/mL. HOMA-IR explains 17% of the variations in serum leptin levels ($R = 0.409$, $R^2 = 0.167$, $P < 0.001$, $F = 12.85$).

2.5.2. Adiponectin

Adiponectin demonstrated inverse correlations with weight, BMI, waist circumference, hip circumference, WHR, GLU 60′, IRI 0′, IRI 60′, IRI 120′, HOMA-IR, TG, TG/HDL-C, and AIP. Conversely, a significant positive relationship between adiponectin and calculated insulin sensitivity indices (QUICKI and Matsuda index) was observed (Table 4).

Table 4. Correlations between adiponectin and anthropometric, metabolic, and lipid parameters.

Parameter	*r*	*p*
Weight	-0.385	0.001
BMI	-0.361	0.003
Waist	-0.411	0.001
Hip	-0.341	0.005

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WHR	-0.317	0.009
GLU 60′	-0.291	0.025
IRI 0′	-0.332	0.006
IRI 60′	-0.288	0.027
IRI 120′	-0.259	0.047
HOMA-IR	-0.308	0.012
MATSUDA	0.408	0.001
QUICKI	0.395	0.001
TG	-0.409	0.01
TG/HDL-C	-0.363	0.003
AIP	-0.422	<0.001

2.5.3. Visfatin

A negative correlation between visfatin and HDL-C was established (r = –0.376, p = 0.024). Furthermore, this adipokine showed a trend toward inverse association with Matsuda index (Kendall's tau = –0.226, p = 0.051).

2.5.4. Resistin

Study results showed positive relationships between resistin and the following glucose and insulin metabolism parameters – GLU 0′ (r = 0.278, p = 0.024), IRI 120′ (r = 0.315 p = 0.015) and HOMA-IR (r = 0.272, p = 0.027). Additionally, resistin was found to be inversely correlated with QUICKI (r = –0.246, p = 0.046) and Matsuda index (r = –0.243, p = 0.050).

3. Discussion

This study provides compelling evidence that IR significantly alters the adipokine profile in women with PCOS, independent of potential confounders such as age and BMI. The observed elevation in leptin, visfatin, and resistin levels, along with decreased adiponectin concentrations, reflects a proinflammatory and metabolically dysregulated phenotype. These findings support the concept that IR is not merely a downstream consequence but also an upstream driver of endocrine and metabolic dysfunction in PCOS, contributing to the amplification of both reproductive and cardiometabolic abnormalities.

Our finding of elevated leptin levels in IR women with PCOS is consistent with numerous previous reports [20,21]. Hyperleptinemia in this context likely reflects a state of leptin resistance, characterized by impaired hypothalamic feedback despite high circulating levels [22]. The strong correlations between leptin and anthropometric indices, HOMA-IR, and QUICKI in our cohort mirror results from Panidis et al. [23] and Nyangasa et al. [24], who also noted leptin's positive associations with markers of central obesity. Additionally, Chakrabarti et al. observed that leptin concentrations were more than 2-fold higher in IR PCOS patients compared with controls and showed strong positive correlations with circulating insulin [25]. Similarly, Jahromi et al. demonstrated robust associations between leptin and HOMA-IR, QUICKI, body weight, and BMI in infertile women with PCOS, identifying HOMA-IR as the most sensitive marker of insulin resistance [26].

In agreement with our data, Daghestani et al. found that leptin correlated positively with BMI, WHR, total cholesterol (TC), LDL-C, and TG, and inversely with HDL-C, with circulating insulin emerging as the strongest determinant of leptin levels [27]. Furthermore, the established positive relationship between leptin and atherogenic lipid ratios (e.g., TG/HDL-C, AIP) aligns with emerging evidence suggesting leptin as an independent predictor of cardiometabolic risk in PCOS [12,28]. Lee et al. reported that TG/HDL-C was significantly higher in PCOS and served as a useful surrogate marker of insulin IR and cardiometabolic risk [29], while Demirci et al. showed that AIP was elevated in PCOS and independently predicted by both PCOS status and HOMA-IR [30].

Experimental data provide further insight into the reproductive interface: in vitro studies in human theca and granulosa cells show that leptin can inhibit IGF-I–mediated augmentation of LH-

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induced androgen and progesterone synthesis at concentrations typical of obesity, suggesting dysregulated ovarian leptin signaling in PCOS [31,32].

Adiponectin, in contrast, exhibited significantly lower concentrations in IR subjects and was positively associated with Matsuda and QUICKI indices, in agreement with several meta-analyses [33,34]. Its inverse correlations with TG and AIP reinforce its recognized anti-atherogenic properties, possibly mediated via AMPK activation, enhanced fatty acid oxidation, and suppression of foam cell formation [19,35]. While low adiponectin is a consistent hallmark of PCOS across most populations [36], some studies have noted that its predictive utility varies by phenotype, obesity status, and ethnicity [37,38].

A systematic review and meta-analysis by Toulis et al. [33] reported that, after controlling for BMI-related effects, adiponectin levels were significantly lower in women with PCOS compared to non-PCOS controls - a finding present in both lean and obese phenotypes. Similarly, Patil et al. [39] observed that serum adiponectin levels were decreased in women with PCOS and inversely associated with BMI, TC, and TG, suggesting potential diagnostic and prognostic value.

The association between adiponectin and IR in PCOS has also been highlighted by Shirazi et al. [40], who demonstrated a significant correlation between insulin levels and the free androgen index independent of obesity. This underscores the central role of IR in PCOS pathophysiology. Phenotypic variations further modulate adiponectin levels, as shown by Barrea et al. [41], who reported that obese PCOS patients exhibited greater prevalence of metabolic and reproductive disturbances compared to lean counterparts, suggesting that obesity and PCOS phenotype influence circulating adiponectin concentrations. In contrast, genetic studies such as that by Nowak et al. [42] found that adiponectin gene polymorphisms (e.g., rs17300539) were not significantly associated with metabolic syndrome in PCOS, indicating that environmental and metabolic factors may play a more prominent role than genetics in determining adiponectin levels in this population.

Visfatin's role in PCOS remains controversial. Initially described as an insulin-mimetic adipokine (nicotinamide phosphoribosyltransferase, NAMPT) [43], subsequent research has highlighted its pro-inflammatory actions through NF-κB activation and upregulation of IL-6 [44]. In our study, increased visfatin levels in IR women, together with negative associations with HDL-C and Matsuda index, suggest that visfatin may contribute both to impaired insulin sensitivity and atherogenic dyslipidemia. Similar associations were reported by Kowalska et al. [45], whereas other studies have found no significant differences in visfatin levels between PCOS phenotypes [46], underscoring the need for stratified analyses based on metabolic status.

Building upon these observations, evidence from a comprehensive meta-analysis encompassing 1,341 women (695 with PCOS and 646 clinically healthy controls) provides further insight into visfatin dynamics in PCOS [47]. The primary objective of this study was to evaluate serum visfatin levels across the two cohorts and to perform a comparative analysis. The results unequivocally demonstrated significantly elevated serum visfatin concentrations in women with PCOS relative to controls. Notably, stratified and univariate analyses revealed no significant associations between heightened visfatin levels and BMI, HOMA-IR, or testosterone concentrations [47]. These findings suggest that elevated circulating visfatin may constitute a distinct intragroup characteristic of PCOS, highlighting the potential utility of this adipokine as a diagnostic biomarker for the syndrome.

El-Said et al. reported significantly elevated plasma visfatin concentrations in a cohort of IR women with PCOS (72.94 ± 33.3 ng/mL) compared with clinically healthy controls (54.69 ± 31.5 ng/mL, $P = 0.039$). Within the PCOS group, visfatin demonstrated positive correlations with BMI, waist circumference, HOMA-IR, and free androgen index (FAI), and inverse correlations with luteinizing hormone (LH), total testosterone, and sex hormone-binding globulin (SHBG). Across the overall study population, plasma visfatin concentrations were inversely associated with HDL-C ($r = -0.349$, $P = 0.013$), highlighting a potential link with atherogenic risk [48]. Interestingly, in contrast to these observations, Gen et al. reported a positive correlation between plasma visfatin and HDL-C in a cohort of women with PCOS who exhibited normal body weight, suggesting that the relationship between visfatin and lipid metabolism may be modulated by metabolic status [49]. Taken together,

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these findings underscore the complexity of visfatin's role in PCOS and emphasize the importance of stratified analyses according to insulin resistance and body composition.

Resistin, although less studied in PCOS, showed positive correlations with fasting/postprandial insulin, and inverse relationships with QUICKI and Matsuda indices. These results are consistent with findings from Estienne et al. [50] and Bril et al. [51], who linked elevated resistin to systemic inflammation, IR, and endothelial dysfunction in PCOS. Similarly, Lewandowski et al. [52] reported that serum resistin levels were significantly higher in PCOS patients compared to BMI-matched controls and correlated with HOMA-IR and markers of subclinical inflammation, supporting a role in metabolic dysregulation. In a study by Yildiz et al. [53], resistin was found to be positively associated with pro-inflammatory cytokines such as TNF-α and CRP, suggesting its involvement in low-grade chronic inflammation characteristic of PCOS. Mechanistically, resistin may impair insulin signaling by upregulating suppressor of cytokine signaling-3 (SOCS-3) and enhancing vascular inflammation [54], while experimental data indicate that resistin can also promote hepatic gluconeogenesis and reduce glucose uptake in adipocytes, further exacerbating insulin resistance [52]. Collectively, these findings suggest that resistin not only reflects metabolic and inflammatory disturbances in PCOS but may also actively contribute to the pathophysiology of insulin resistance and cardiometabolic risk in this population.

Our data support the hypothesis that adipokine dysregulation in PCOS is closely linked to IR, adiposity, systemic inflammation, and lipid abnormalities, all of which synergistically contribute to an elevated cardiometabolic risk profile [55]. Notably, we extend prior knowledge by demonstrating that specific adipokines—particularly leptin and adiponectin—correlate with composite atherogenic indices such as AIP, which are seldom evaluated in PCOS research.

From a clinical perspective, these results highlight the potential value of adipokine profiling in early risk stratification and phenotype-specific management of PCOS. Interventions targeting IR—such as metformin, inositol isomers, and GLP-1 receptor agonists—have been shown to modulate adipokine levels and improve metabolic and reproductive outcomes [56–58]. Likewise, lifestyle interventions focusing on weight reduction, physical activity, and dietary patterns with low glycemic load or anti-inflammatory potential have demonstrated beneficial effects on adipokine balance and cardiometabolic markers [59,60].

Nevertheless, certain limitations should be acknowledged. The cross-sectional nature of the study precludes causal inference, and circulating adipokine concentrations may not fully reflect tissue-specific activity or receptor sensitivity. Moreover, we did not assess genetic variants in adipokine-related genes, which may influence individual responses. Future longitudinal and interventional studies are warranted to clarify the causal pathways linking adipokine changes with long-term cardiovascular and reproductive outcomes in PCOS.

4. Materials and Methods

4.1. Study Design and Population

This cross-sectional, observational study included 150 women aged 18–35 years, diagnosed with polycystic ovary syndrome (PCOS) according to the Rotterdam criteria (2003) [2]. Participants were recruited from the Clinic of Endocrinology and Metabolic Diseases at "Sv. Georgy" Uviversity Hospital of Plovdiv between June 2020 and June 2023. The diagnosis of PCOS required at least two of the following: oligo/anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound, with exclusion of other etiologies (e.g., congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumors, thyroid dysfunction, and hyperprolactinemia).

Exclusion criteria included: chronic inflammatory or autoimmune disorders, current use of hormonal or insulin-sensitizing medications, and pregnancy.

Participants were stratified into two groups based on insulin resistance (IR) status: 1. PCOS group without IR (n = 74), and 2. PCOS group with IR (n = 76), defined by HOMA-IR ≥ 2.5 [61].

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4.2. Anthropometric and Clinical Measurements

Anthropometric evaluation included body weight, height, waist circumference (W), and hip circumference (H), measured using standard techniques. Waist circumference was determined after the act of expiration measuring the area between the bottom edges of the ribs and the iliac crests. Hip circumference was assessed at the level of the greater trochanters. Body mass index (BMI) {weight (kg)/height² (m²)} and Waist-to-hip ratio (WHR) were calculated.

4.3. Biochemical, Hormonal and Adipokine Assessment

Venous blood for laboratory tests was taken under standard conditions − early in the morning, after an overnight 12-hour fast period, during the follicular phase of the menstrual cycle (2nd to 5th day after a spontaneously obtained menstrual cycle) or 7 days after gestagen-induced bleeding. A 75 g oral glucose tolerance test (OGTT) was performed with blood sampling at 0, 60, and 120 minutes for plasma glucose (GLU) and insulin (IRI) levels. Samples for determination of GLU and IRI, lipid parameters, standard hormonal parameters and adipokines were taken to the Central Clinic Laboratory, "Sv. Georgy" University Hospital of Plovdiv, Bulgaria.

Serum insulin levels were determined using a chemiluminescent immunoassay (CLIA) kit from Beckman Coulter, Inc., Ireland. This sandwich immunoassay method showed the following characteristics: dilution recovery - 96–104%; sensitivity - 0.03 μIU/mL; intra-assay variation (CV) - 2.0–4.2%; inter-assay variation (CV) - 3.1–5.6%; specificity - no cross-reactivity with bilirubin (10 mg/dL), triglycerides (20.32 mmol/L), or C-peptide (20,000 pmol/L) was observed; reference range: 1.9–23.0 μIU/mL. Serum glucose levels were tested by a standard GOD-POD method.

Insulin resistance and sensitivity were evaluated using the following indices: HOMA-IR = (Fasting insulin [μU/mL] × Fasting glucose [mmol/L]) / 22.5; QUICKI = 1 / (log fasting insulin [μU/mL] + log fasting glucose [mg/dL]); Matsuda index = 10,000 / √[(Fasting glucose [mg/dL] × Fasting insulin [μU/mL]) × (Mean OGTT glucose × Mean OGTT insulin)].

Serum lipids were measured enzymatically. Concentrations of total cholesterol (TC) were determined by ChOD, PAP; those of TG − by GPO, PAP and HDL-C - by MgSO4-dextran SO4 precipitation, Schneiders Analysers; Netherlands test; Delta Kone Autoanalyser**.** LDL-C was calculated using Friedewald formula. Calculated atherogenic indices included the TG/HDL-C ratio, LDL-C/HDL-C ratio, and the Atherogenic Index of Plasma (AIP), which is defined as $\log_{10}$ of the TG/HDL-C ratio.

Serum leptin levels were quantified by a solid-phase human ELISA method using a commercial kit from DRG, Germany with the following characteristics: sensitivity - 0.2 ng/mL; intra-assay CV < 8.7%; inter-assay CV < 5.4%. Serum adiponectin concentrations were determined using a human ELISA kit from BioVendor, Heidelberg, Germany with the following features: sensitivity - 26 ng/mL; intra-assay CV < 5.9%; inter-assay CV < 7.0%. Visfatin concentrations were measured by ELISA using a kit from Gentaur Molecular Products, Kampenhout, Belgium (catalog No. CSB-E08940h) with: sensitivity - 0.16 ng/mL; intra-assay CV 4.0–6.0%; inter-assay CV 8.0–12.0% and specificity - no detected cross-reactivity with similar proteins. Levels of serum resistin were measured by a competitive solid-phase human EIA using a kit from PHOENIX PHARMACEUTICAL INC, USA characterized by sensitivity: 1.16 ng/mL; Intra-assay CV < 14.0%; inter-assay CV < 5.0%.

4.4. Statistical Analysis

All statistical analyses were conducted using SPSS software, version 21.0 for Windows. The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Resistin levels were $\log_{10}$-transformed prior to analysis to achieve a normal distribution. Data for normally distributed variables were presented as mean ± standard deviation (SD), whereas non-normally distributed variables were expressed as median and interquartile range. Group comparisons were performed using independent sample t-tests or the Mann–Whitney U test, as appropriate. Correlation analyses employed Pearson, Spearman, or Kendall's tau correlation coefficients, depending on the data type and distribution. Stepwise linear regression models were applied to identify predictors of leptin

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levels and to explore associations between adipokines and insulin resistance. A two-tailed p-value < 0.05 was considered statistically significant. No imputation was performed for missing data.

5. Conclusions

This study underscores the presence of a distinct metabolic and inflammatory adipokine profile in women with PCOS and insulin resistance. Elevated serum levels of leptin, visfatin, and resistin, alongside reduced adiponectin concentrations, were strongly associated with markers of impaired glucose metabolism, increased adiposity, and adverse atherogenic indices. These findings suggest that adipokine dysregulation not only reflects underlying metabolic dysfunction, but may actively contribute to the progression of cardiometabolic risk in insulin-resistant PCOS phenotypes.

The observed correlations between adipokines and insulin resistance/sensitivity indices (HOMA-IR, QUICKI, Matsuda), as well as atherogenic ratios such as TG/HDL-C and AIP, reinforce their potential utility as integrated biomarkers for metabolic risk stratification in PCOS. Moreover, the data point toward adipocytokines as plausible therapeutic targets in the management of this heterogeneous disorder.

Future studies should focus on longitudinal follow-up and mechanistic investigations to determine whether modifying adipokine profiles through pharmacological or lifestyle interventions can translate into improved metabolic, reproductive, and cardiovascular outcomes in women with PCOS.

6. Patents

The authors declare that there are no patents resulting from this work.

Author Contributions: Conceptualization, D.K. and M.I..; methodology, D.K.; software, D.K.; validation, D.K., M.I. and M.O.; formal analysis, T.D.; investigation, T.D.; resources, M.O.; data curation, M.I.; writing—original draft preparation, D.K.; writing—review and editing, M.O.; visualization, T.D.; supervision, M.O.; project administration, D.K. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of MEDICAL UNIVERSITY OF PLOVDIV (protocol code 2444/26.10.2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to ethical restrictions and participant confidentiality, the dataset is not publicly available.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

PCOS	Polycystic Ovary Syndrome
IR	Insulin Resistance
BMI	Body Mass Index
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
QUICKI	Quantitative Insulin Sensitivity Check Index
AIP	Atherogenic Index of Plasma
HDL-C	High-Density Lipoprotein Cholesterol
LDL-C	Low-Density Lipoprotein Cholesterol

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TG	Triglycerides
ELISA	Enzyme-Linked Immunosorbent Assay
IL-6	Interleukin 6
OGTT	Oral Glucose Tolerance Test

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