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Review

Adipocytokines in polycystic ovary syndrome (PCOS): A systematic review and meta-analysis

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Abstract: The central tenet in PCOS is predicting the development of the development of metabolic syndrome is Insulin resistance (IR). Adipocytokines are hormones produced by adipose cells that help to regulate insulin secretion and resistance in the body. This study discusses the effect of different adipocytokines and their patterns (increased or reduced) in predicting insulin resistance in obese and lean PCOS patients. A systematic review and meta-analysis were performed which identified relevant studies from 2010 to 2020. Data was analyzed using Review Manager Version (RevMan) 5.4 software. A fixed-effect model was fitted to estimate the pooled effect of adipocytokines. I^2 test statistics were done to test the heterogeneity of included studies. Of 17 selected studies with 1504 participants, there is considerably lower levels of adiponectin among women with PCOS as compared with healthy controls with mean difference of −3.79 (95% CI = 3.97–3.60, I^2 = 73%; P = 0.005). In comparison to their healthy counterparts, leptin levels were shown to be higher in women with PCOS with mean difference of 3.64 (95% CI = 3.20–4.08, I^2 = 97%; P = 0.00001). Leptin concentration was shown to be directly related to IR and BMI. After controlling for BMI and age-related effects, adiponectin levels appear to be lower in women with PCOS compared to non-PCOS controls but leptin levels appear to be higher. In conclusion, increased in adipocytokines such as leptin, visfatin and chemerin predict IR among both obese and lean PCOS whereas decreased levels of zinc-alpha2 glycoprotein predict IR. Adipocytokines can be potential predictive serum biomarkers of insulin resistance (IR) in PCOS.

Keywords: polycystic ovary syndrome; adipocytokines; insulin resistance

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common hormonal disorder affecting women of adolescent and reproductive age group. The characteristics of PCOS include hyperandrogenism, ovulatory dysfunction and polycystic ovaries [1]. Metabolic problems such as Type 2 diabetes mellitus (T2DM), Insulin resistance (IR) and adipose tissue malfunction are common in PCOS patients [2]. It is estimated that 50–70% of patients with PCOS have insulin resistance and central obesity [3]. Insulin has both direct and indirect functions in the pathophysiology of hyperandrogenaemia in PCOS women. Insulin and LH work together in the ovary to stimulate the synthesis of androgen by the theca cells. Insulin also suppresses SHBG production in the liver, resulting in an increase in the quantity of unbound (free) or bioactive testosterone in the bloodstream and an enhancement in the impact of circulating androgens [4]. IR is a condition in which a given insulin dose has a lesser biological effect than expected [5]. Obesity, diabetes, glucose intolerance and metabolic syndrome are all examples of insulin resistance syndromes. Burghen et al. first demonstrated the presence of IR in PCOS women [6]. Measuring IR is not always simple and precise. Gold standard test such as hyperinsulinemic euglycemic glucose clamp is a reliable, but complex invasive directly measuring all glucose disposal under steady-state insulin conditions [7]. The less precise but more simple test include homeostasis model assessment (HOMA) which determines IR and pancreatic β-cell function from basal glucose and insulin (or C-peptide) levels, quantitative insulin sensitivity check index (QUICKI) and oral glucose tolerance test (OGTT). However, none of these tests can reflect the body's dynamic insulin cycle accurately [8]. As a result, novel surrogate biomarkers are required for a more reliable assessment of insulin metabolism.

Adipocytokines, are hormones, cytokines, or glycoproteins produced by adipose tissue that have both pro-inflammatory and anti-inflammatory properties. They signal vital organs to maintain metabolic homeostasis and are employed in cellular crosstalk between cells [9]. Metabolic disorders can arise from any pathway malfunction. Leptin, adiponectin, omentin-1, visfatin, chemirin, fetuin-A and meteorin-like protein (Metrnl) are examples of adipocytokines reported in literature. Changes in serum concentrations of these biomarkers have proved beneficial in determining the function and distribution of adipose tissue [10]. Several studies suggest that reduced blood levels of adiponectin and higher leptin concentration are additional signs of metabolic syndrome or cardiovascular disease [11]. Furthermore, adiponectin and high-density lipoprotein (HDL) levels are positively correlated [12–15]. Omentin is a glycoprotein that enhances insulin sensitivity in adipocytes and is produced and released from visceral but not subcutaneous adipose tissue. Omentin-1, the most common circulating isoform, is negatively linked to BMI, waist circumference, serum leptin levels and insulin resistance syndrome [16]. Given the relevance of insulin resistance and obesity in PCOS, various studies have been conducted to determine the systemic levels of adipocytokines [17]. The functionality and/or distribution of adipose tissue can be assessed using changes in circulating adipokine levels. These variations might result from increased visceral fat in women with PCOS which can occur even with a normal BMI explaining PCOS's typical insulin resistance even in lean PCOS patients [18].

Adipocytokines have been demonstrated to have a crucial function in the aetiology of obesity and obesity-related illnesses in studies [7]. These findings led to the research question of whether

adipocytokines can predict insulin resistance in PCOS. A systematic review and metanalysis was undertaken to determine the link between adipocytokine levels and insulin resistance in both obese and lean PCOS patients. The review highlights both common and new adipocytokines as well as their patterns of association (increased or decreased) in PCOS patients.

2. Materials and methods

A literature search was conducted through the electronic databases PubMed, Medline, and Cochrane central digital (CENTRAL) for studies published from January 2010 to December 2020. Boolean operators and MeSH terms were combined along with relevant truncations to create the following search query, "Polycystic Ovary Syndrome" AND "Insulin Resistance" AND "Adipocytokine*". A review of the reference lists of chosen articles was conducted to confirm that no relevant studies were overlooked.

2.1. Study selection

To ensure that they were suitable for further evaluation, specific criteria were established to separate relevant research from the initial publications retrieved. We included all observational studies which reported any adipocytokines in heathy controls compared to women with PCOS diagnosed according to either Rotterdam criteria (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004) or National Institute of Health (NIH) criteria (Zawadzki and Dunaif, 1992). We excluded articles about case reports, case series and letters to the editor, animal studies, studies where participants were not diagnosed using NIH/Rotterdam criteria and studies not reported in English language. The selection procedure, involved record identification, record screening and record eligibility assessment which has been represented using a PRISMA flow chart as shown in Figure 1.

2.2. Data extraction and synthesis

In a piloted data extraction form, two independent investigators collected information from included studies individually. The title, study design, first author, publication year, sample size, country of study, mean age of participants, mean BMI of participants and summary of study results were all gathered from individual studies.

2.3. Risk of bias assessment

The methodological quality of observational studies of identified case-control studies was assessed using a tool to determine how well each research had addressed the potential risk of bias present. All case-control studies were assessed using the Newcastle-Ottawa scale by Wells et al. [18]. The analysis of risk assessment is presented in Table 1.

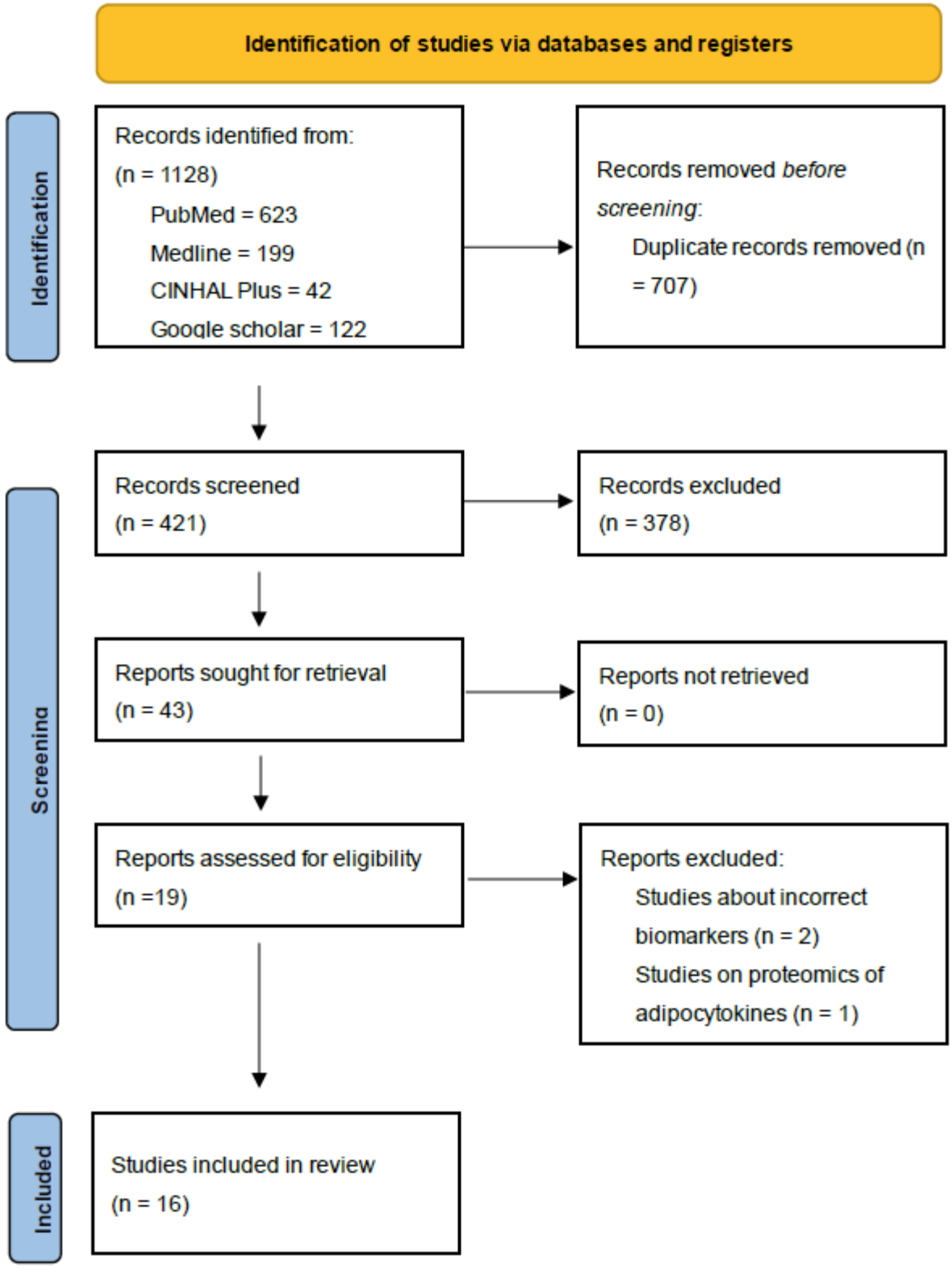

Figure 1. PRISMA flow chart.

Table 1. Assessment of study quality using Newcastle-Ottawa Scale (NOS).

Title	Selection	Comparability	Exposure	Total Score
1. Fatima Zahraa Fouani et al. 2020	****	**	***	9
2. Sha Liu et al. 2020	***	**	***	9
3. Murat Gozukucuk 2020	***	**	***	8
4. Daniel H Kort et al. 2015	***	**	***	8
5. Recep Yildizhan et al. 2011	**	**	***	7
6. Dooddappa Bannigida et al. 2018	***	**	***	8
7. Chenchen Tang et al. 2019	***	**	***	8
8. Shiyuan Yang et al. 2016	****	**	***	9
9. Hyun-Young Shin et al. 2011	****	**	***	9
10. Mohamed El-Gharib et al. 2015	***	**	***	8
11. Cankaya S 2014	****	**	***	9
12. Sharifi F 2010	***	**	***	8
13. Li H et al. 2015	**	**	***	7
14. Mirza SS et al. 2014	**	**	***	7
15. Namavar Jahromi B et al. 2017	****	**	***	9
16. Baig M et al. 2014	****	**	***	9
17. Gowthami P 2019	***	**	***	8

Note: Good quality: 3 or 4 stars in selection domain; Fair quality: 2 stars in selection domain; Poor quality: 0 or 1 star in selection domain or 0 stars in comparability domain.

2.4. Statistical analysis

For meta-analysis RevMan 5.4 software was utilised. The difference in significant adipocytokine levels between PCOS patients and healthy controls will be the predicted outcome of this investigation. The I^2 test and Cochran's chi-square-based Q statistic test were calculated to analyse potential heterogeneity amongst the studies.

The Joint-Committee on Research and Ethics Meeting of the International Medical University (IMU) authorised this study protocol [BMSc I-2021(07)].

3. Results

Using the baseline screening approach, a total of 1128 potential studies were found including 623 articles from PubMed, 199 from MEDLINE, 42 from CINHAL plus, 122 from google scholar and 142 studies from Cochrane central. After deleting the duplicates a total of 421 studies were gathered. We excluded 378 papers after a thorough study of their abstracts and 19 full-text papers were retrieved. Upon reviewing 19 full texts three studies were eliminated based on the inclusion/exclusion criteria and 17 articles were included in the qualitative synthesis and statistical analysis. A total of 1504 study participants were analysed. The characteristics of included studies are shown in Table 2.

3.1. Geographical distribution of studies

The papers that were pooled together were from across the world. A similar number of studies came from the Middle East [19–22] and the Asian subcontinent [23–26]. Two studies were from Turkey [27,28] and one was from the United States [20].

3.2. Association of adipocytokines and PCOS is as presented in Tables 3 and 4

1. Leptin: Leptin levels in the PCOS group were substantially greater than in the controls ($P = 0.001$). Fasting, HOMA-IR and leptin levels were found to be positively associated [19,27–30].
2. Omentin-1: In the PCOS group, serum omentin-1 levels were considerably lower than in the controls ($P < 0.0001$) [20].
3. Chemerin: Chemerin levels in the PCOS group were higher but not statistically significant [20,29].
4. Visfatin: When obese women with PCOS were compared to their respective controls serum levels of visfatin were higher in obese women with PCOS than in lean women with PCOS with $P < 0.001$, indicating a positive association between visfatin and obesity indices (BMI) [21].
5. Fetuin A: Fetuin-A levels in the blood were greater in PCOS patients than in healthy women. Fetuin-A concentrations were substantially greater in the obese group than in the lean group. There was no significant difference in serum fetuin-A levels when healthy women were separated into overweight and lean groups suggesting that there was no link between serum fetuin-A levels in overweight or healthy women [22].
6. ZAG: The levels of circulating ZAG in PCOS patients were lower than in healthy controls $P < 0.05$. When HOMA-IR scores were considered, the levels of circulating ZAG were shown to be linked to hyperandrogenism, implying that circulating ZAG levels are linked to IR [23].
7. Metrnl: The difference in serum metrnl levels between the control and PCOS groups remained significant after accounting for variables (age and BMI) ($P < 0.001$). BMI was inversely associated to serum metrnl levels. It had a negative correlation with HOMA-IR in the PCOS group and subgroups [22].
8. Adiponectin: The levels of adiponectin were shown to be inversely linked with BMI. Independent of IR, adiponectin levels were shown to be considerably lower in both obese and non-obese women with PCOS when compared to their respective controls indicating a negative association between adiponectin and obesity [19,21,29,30].

Table 2. Characteristics of studies.

	Study title	Author, Year, Country	Sample size	PCOS diagnostic criteria	Age PCOS vs Controls	BMI (kg/m^2) PCOS vs Controls	Findings
1	Circulating levels of meteorin-like protein in polycystic ovary syndrome: A case-control study [22]	Fouani F et al., 2020, Iran	120 PCOS vs 60 controls	Rotterdam criteria	29.88 ± 4.22 vs 30.02 ± 4.60	26.01 ± 3.39 vs 25.48 ± 3.26	↓ Metrnl, ↓ adiponectin PCOS vs controls. Both biomarkers correlated with HOMA-IR
2	Serum Fetuin-A levels are increased and associated with insulin resistance in women with polycystic ovary syndrome [19]	Liu S et al., 2020, China	122 PCOS vs 85 controls	Rotterdam criteria	25.3 ± 3.4 vs 26.0 ± 3.4	24.4 ± 4.4 vs 21.6 ± 2.9	↑ Fetuin A PCOS vs controls
3	Adiponectin and leptin levels in normal weight women with polycystic ovary syndrome [29]	Gozukucuk M et al., 2020, Turkey	40 PCOS vs 40 controls	Rotterdam criteria	24.15 ± 3.570 vs 24.50 ± 3.289	23.18 ± 3.087 vs 23.30 ± 3.385	↑ Leptin, ↓ adiponectin PCOS vs controls. Both biomarkers correlated with HOMA-IR

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	Study title	Author, Year, Country	Sample size	PCOS diagnostic criteria	Age PCOS vs Controls	BMI (kg/m^2) PCOS vs Controls	Findings
4	Chemerin as a marker of body fat and insulin resistance in women with polycystic ovary syndrome [20]	Kort D et al., 2015, USA	22 PCOS vs 23 controls	Rotterdam criteria	38 ± 4.3 vs 27 ± 5.4	33.2 ± 0.86 vs 23.4 ± 0.86	↓ Omentin-1 PCOS vs controls but no correlation with HOMA-IR
5	Serum retinol-binding protein 4, leptin, and plasma asymmetric dimethylarginine levels in obese and nonobese young women with polycystic ovary syndrome [27]	Yildizhan R et al., 2011, Turkey	57 PCOS vs 27 controls	Rotterdam criteria	27.19 ± 1.73 obese PCOS, 25.70 ± 3.70 lean PCOS vs 25.44 ± 2.62 controls	30.32 ± 3.71 obese PCO, 23.85 ± 1.1 lean PCOS vs 23.88 ± 3.83 controls	↑ Leptin, PCOS vs controls (more in obese than lean PCOS). The biomarker correlated with HOMA-IR
6	Serum visfatin and adiponectin - markers in women with polycystic ovarian syndrome [21]	Bannigida D et al., 2018, India	100 PCOS vs 100 controls	Rotterdam criteria	Unavailable	35.7 ± 3.05 obese PCOS, 25.6 ± 2.53 lean PCOS vs 32.2 ± 4.39 obese controls, 21.2 ± 4.86 lean controls	↑ Visfatin, ↓ adiponectin PCOS vs controls (more in obese than lean PCOS). Both biomarkers correlated with HOMA-IR

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	Study title	Author, Year, Country	Sample size	PCOS diagnostic criteria	Age PCOS vs Controls	BMI (kg/m^2) PCOS vs Controls	Findings
7	Association between circulating zinc-alpha2-glycoprotein levels and the different phenotypes of polycystic ovary syndrome. [23]	Tang C et al., 2020, China	100 PCOS vs 99 controls	Rotterdam criteria	25.7 ± 4.4 Classic, 25.8 ± 4.7 Normoandrogenic, 25.1 ± 3.4 Ovulatory, 26.6 ± 4.5 no-PCOM vs 25 controls	25.5 ± 4.0 classic, 23.1 ± 4.3 Normoandrogenic, 28.1 ± 5.1 ovulatory, 24.7 ± 4.9 no-PCOM vs 20 controls	↓ Zinc-alpha2-glycoprotein PCOS vs controls. The biomarker correlated with HOMA-IR
8	Are serum chemerin levels different between obese and non-obese polycystic ovary syndrome women? [28]	Yang S et al., 2016, China	118 PCOS vs 114 controls	Rotterdam criteria	25.07 ± 4.27 vs 24.62 ± 3.69	28.28 ± 2.41 Obese PCOS, 20.86 ± 2.16 lean PCOS vs 26.27 ± 1.26 Obese controls, 20.10 ± 1.26 lean controls	↑ Chemrin PCOS vs controls. The biomarker correlated with HOMA-IR
9	Adiponectin in Women with Polycystic Ovary Syndrome [24]	Shin H et al., 2011, South Korea	60 PCOS vs 80 controls	Rotterdam criteria	29.0 ± 3.9 vs 30.5 ± 5.4	25.1 ± 5.5 vs 25.0 ± 3.3	↓ Adiponectin PCOS vs controls. The biomarker correlated with QUICKI

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	Study title	Author, Year, Country	Sample size	PCOS diagnostic criteria	Age PCOS vs Controls	BMI (kg/m^2) PCOS vs Controls	Findings
10	Correlation Between Insulin, Leptin and Polycystic Ovary Syndrome [30]	Gharib M El et al., 2015, Egypt	75 PCOS vs 50 controls	Rotterdam criteria	25.5 ± 3.9 vs 24.0 ± 3.7	24.3 ± 3.6 vs 25.7 ± 2.5	↑ Leptin PCOS vs controls. The biomarker correlated with HOMA-IR
11	Insulin resistance and its relationship with high molecular weight adiponectin in adolescents with polycystic ovary syndrome and a maternal history of polycystic ovary syndrome [31]	Cankaya S 2014	40 PCOS vs 40 controls	Rotterdam criteria	21.5 ± 2.8 vs 23.0 ± 3.1	1.71. ± 0.72 vs 4.17 ± 2.0	↓ Adiponectin PCOS vs controls. The biomarker correlated with HOMA-IR

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	Study title	Author, Year, Country	Sample size	PCOS diagnostic criteria	Age PCOS vs Controls	BMI (kg/m^2) PCOS vs Controls	Findings
12	Decreased adiponectin levels in polycystic ovary syndrome, independent of body mass index [32]	Sharifi F 2010, Iran	103 PCOS vs 73 controls	Rotterdam criteria	23.07 ± 2.27 vs 25.62 ± 4.2	8.4 +/− 2.7 ng/mL vs 13.6 +/− 5 ng/mL	Group I (normal nonlean women); group II (normal lean women); group III (nonlean women with PCOS); and group IV (lean women with PCOS) ↓ adiponectin levels were reduced in all the women with PCOS that was independent of body mass index
13	A case-control study of correlation between serum adiponectin levels and polycystic ovary syndrome [33]	Li H et al., 2015 Chinese	97 PCOS vs 116 controls	Rotterdam criteria		21 ± 16 mg/L vs 25 ± 13 mg/L	↓ Adiponectin levels in the women with PCOS is correlated with PCOS per se, independent of insulin resistance and obese.
14	Association between circulating adiponectin levels and polycystic ovarian syndrome [34]	Mirza SS et al., 2014, Pakistan	75 PCOS vs 75 controls	Rotterdam criteria	16–35	OR = 3.2, 95% CI 1.49–6.90, P-value 0.003	↓ Adiponectin levels in the women with PCOS.

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	Study title	Author, Year, Country	Sample size	PCOS diagnostic criteria	Age PCOS vs Controls	BMI (kg/m^2) PCOS vs Controls	Findings
15	Association of leptin and insulin resistance in PCOS [35]	Jahromi NB et al., 2017	99 PCOS with infertility vs 90 controls	Rotterdam criteria	27.64 ± 4.34 vs 29.35 ± 5.95	41.79 ± 187.89 vs 19.38 ± 12.57	↑ Leptin PCOS vs controls.
16	Serum leptin levels in polycystic ovary syndrome and its relationship with metabolic and hormonal profile in pakistani females [36]	Baig M et al., 2014	62 PCOS vs 90 controls	Rotterdam criteria	29.94 ± 2.51 vs 28.87 ± 3.14	45.56 ± 1.49 vs 41.78 ± 1.31	No significant difference found in circulating leptin concentration between PCOS and NC subjects. A strong correlation of leptin with BMI was observed in both groups
17.	Study of serum adiponectin levels in women with polycystic ovary Syndrome [37]	Gowthami P 2019	62 PCOS vs 90 controls	Rotterdam criteria	20.66 ± 2.62 vs 20.90 ± 2.39	4.56 ± 2.98 vs 7.16 ± 3.28	↓ Adiponectin levels in the women with PCOS. The biomarker correlated with HOMA-IR

Note: PCOS: Polycystic ovary syndrome; BMI : Body Mass Index; Metrnl: Meteorin-like protein; HOMA-IR: Homeostasis model assessment-Insulin resistance; ↓: Decrease; ↑: Increase; NC: Normal controls.

Table 3. Adipocytokine upregulation in obese and lean PCOS vs Controls.

	PCOS BMI < 25 kg/m^2	Controls BMI < 25 kg/m^2	PCOS BMI > 25 kg/m^2	Controls BMI > 25 kg/m^2	HOMA-IR compared to controls
Leptin [19,27–30]	↑↑	↑	↑↑↑	↑	↑
Chemrin [20,29]	↑↑↑	↑	↑↑	↑↑	↑
Visfatin [21]	↑↑↑	↑↑	↑↑↑↑	↑	↑
Fetuin-A [22]	↑↑	↑	↑↑↑↑	↑	↑

Note: ↑: Mildly increase; ↑↑: Moderately increased; ↑↑↑ and ↑↑↑↑: Highly increased; PCOS: Polycystic ovary syndrome; HOMA-IR: Homeostasis model assessment-Insulin resistance; BMI: Body Mass Index.

Table 4. Adipocytokine downregulation in obese and lean PCOS vs Controls.

	PCOS BMI < 25 kg/m^2	Controls BMI < 25 kg/m^2	PCOS BMI > 25 kg/m^2	Controls BMI > 25 kg/m^2	HOMA-IR compared to controls
Adiponectin [19,20,24,29]	↓↓↓	↓↓	↓↓↓↓	↓	↑
Zinc-alpha2-glycoprotein [23]	↓↓↓	↓	↓↓↓	↓	↑
Metrnl [22]	↓	↑	↓↓	↑↑	↑
Omentin-1 [20]	↓↓	↓	↓↓	↓	No correlation

Note: ↓: Mildly decreased; ↓↓: Moderately decreased; ↓↓↓ and ↓↓↓↓: Highly decreased; ↑: Mildly increase; ↑↑: Moderately increased; PCOS: Polycystic ovary syndrome; HOMA-IR: Homeostasis model assessment-Insulin resistance; Metrnl: Meteorin-like protein; BMI: Body Mass Index.

3.3. Adipocytokines and Insulin resistance as seen in Table 5

Regarding adipocytokines and IR, leptin exhibited a positive correlation with HOMA-IR implying that a rise in leptin levels will raise IR in all women with PCOS. However, their association with insulin resistance is only based on the individual report of each paper and thus not supported by the novel analysis of this current report. IR appears to be predominantly more elevated in obese women with PCOS than it is in lean women with PCOS. Visfatin concentrations show a similar pattern with the association of HOMA-IR being twice as high in obese women with PCOS than it is in lean women with PCOS. A similar finding is noted with chemrin, with a threefold increase in IR compared to lean PCOS patients. However, ZAG is dramatically downregulated implying that as serum ZAG concentrations drop the degree of IR rises.

Table 5. Correlation of adipokines and insulin resistance.

Adipocytokines	HOMA-IR in Obese PCOS	HOMA-IR in Lean PCOS
Leptin ↑ [20,27–30]	↑↑	↑
Visfatin ↑ [21]	↑↑	↑
Chemrin ↑ [20,29]	↑↑↑	↑
Zinc-alpha2-glycoprotein ↓ [23]	↑↑↑	↑

Note: ↑: Mildly increase; ↑↑: Moderately increased; ↑↑↑ and ↑↑↑↑: Highly increased; HOMA-IR: Homeostasis model assessment-Insulin resistance; PCOS: Polycystic ovary syndrome.

3.4. Adiponectin levels in PCOS vs control

The meta-analysis in the Figure 2 displays the mean difference in levels of adiponectin in PCOS compared to control in five studies The pooled date included 758 samples (PCOS = 374 vs control = 384). While the I^2 is 73% advocating that heterogeneity amongst the individual studie' is moderate. The analysis suggest that adiponectin is decreased in PCOS women compared to healthy controls with 95% confidence interval (CI) and P-value < 0.00001.

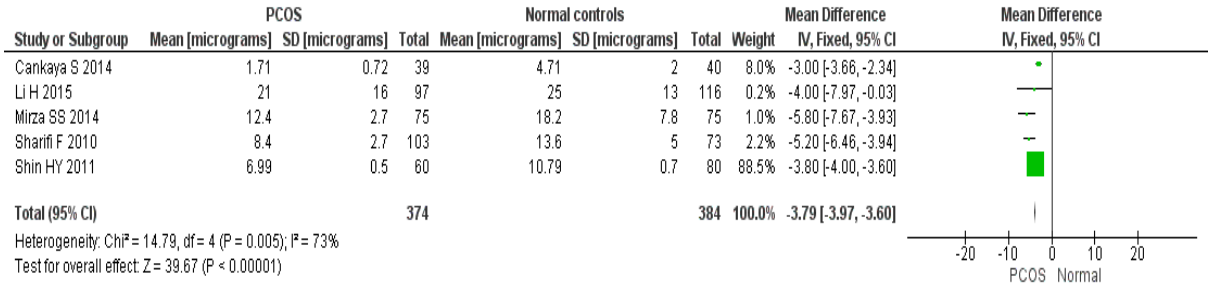

Figure 2. Forest plot of the meta-analysis for studies of adiponectin levels in PCOS versus the control group.

3.5. Leptin levels in PCOS vs control

The meta-analysis in the Figure 3 displays the mean difference in levels of leptin levels in PCOS compared to controls in three studies. The pooled data included 575 samples (PCOS = 236 women vs control = 239 case-controls). Although elevated leptin is significant among PCOS women compared to healthy controls, I^2 is 97% implicating high heterogeneity amongst the individual studies.

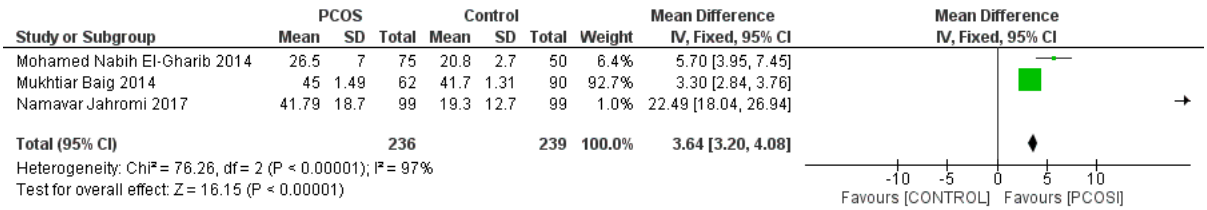

Figure 3. Forest plot of the meta-analysis for studies of leptin levels in PCOS versus the control group.

4. Discussion

The objective of this systematic review which included sixteen papers, concluded that in PCOS women had lower levels of adiponectin, ZAG and omentin-1 and higher levels of leptin, visfatin and chemerin. During the last twenty years, several trials have looked at the circulating quantities of adipocytokines in obese and lean PCOS patients [33,34]. The outcomes of investigations were inconsistent because adipokine levels varied by geographical location, race and age. Given that adipokine levels have been linked to BMI in prior research and there is evidence that PCOS patients have a higher BMI the shift in adipokine levels might be due to obesity rather than PCOS [35,36]. Patients with PCOS with high adipocytokines may develop metabolic syndromes such as Type 2 diabetes mellitus, hypertension and coronary heart disease [36]. PCOS patients have nearly ten times the risk of developing type 2 diabetes as the general population [37,24].

Our findings support the clinical utility adipocytokines levels in predicting IR and initiating appropriate actions in prevention of metabolic syndrome. It has been hypothesized that metformin might alleviate symptoms of PCOS by correcting abnormal levels of certain adipocytokines [25,38]. In this systematic review we included the studies on non-obese PCOS patients which excludes the effect of BMI on PCOS and directly analyse the association of PCOS and adipocytokines.

The main strength of this systematic review is comprehensive literature search to find specific papers on adipocytokines in PCOS and their relationship with IR. This study investigated and characterized both conventional and new adipocytokines in obese and lean PCOS patients. The findings support the existing literature on two common adipocytokines, adiponectin and leptin levels and their association with PCOS patients and IR in comparison to healthy controls [25,38]. We have also appraised other individual adipocytokines adjusted for age and BMI, broadening the perspective of such biomarkers in screening for metabolic syndromes in PCOS [25].

This systematic review identifies certain limitations. Firstly, the sample size differences between experiments may have influenced the findings of a few adipokine correlations. Most studies reported small sample size overall when further subcategorised (obese/lean). There are opportunities to further expand this review within PCOS.

5. Conclusions

There are various tests exists to assess insulin resistance, however, the aim is to achieve a more reliable prediction of insulin metabolism. This review highlights the role of serum biomarkers in determining of IR among PCOS women. Despite the considerable heterogeneity between individual

studies, statistical interpretation reveals a close link between IR and adipocytokines in PCOS patients and controls which might be extrapolated to the conclusion that adipocytokines are inherent to PCOS. In clinical setting adipokine estimation in women with PCOS can be used as a reliable screening tool for predicting insulin sensitivity and anticipate the diagnosis of metabolic and cardiovascular consequences in PCOS. This is further expected to improve the efficient utilisation of medical resources and reduce costs and impact on health economics. However, further large-scale studies are necessary to better clarify the role of these proteins with insulin resistance in this syndrome and integrate into practice guidelines.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

All authors declare no conflicts of interest in this paper.

References

1. Amato MC, Vesco R, Vigneri E, et al. (2015) Hyperinsulinism and polycystic ovary syndrome (PCOS): role of insulin clearance. *J Endocrinol Invest* 38: 1319–1326. https://doi.org/10.1007/s40618-015-0372-x
2. Lin K, Sun X, Wang X, et al. (2021) Circulating adipokine levels in nonobese women with polycystic ovary syndrome and in nonobese control women: A systematic review and meta-analysis. *Front Endocrinol* 11: 537809. https://doi.org/10.3389/fendo.2020.537809
3. Salley KE, Wickham EP, Cheang KI, et al. (2007) Glucose intolerance in polycystic ovary syndrome—a position statement of the Androgen Excess Society. *J Clin Endocrinol Metab* 92: 4546–4556. https://doi.org/10.1210/jc.2007-1549
4. Lee T, Rausch M (2012) Polycystic ovarian syndrome: role of imaging in diagnosis. *Radiographics* 32: 1643–1657. https://doi.org/10.1148/rg.326125503.
5. Chen T, Wang F, Chu Z, et al. (2019) Serum CTRP3 levels in obese children: a potential protective adipokine of obesity, insulin sensitivity and pancreatic β cell function. *Diabetes Metab Syndr Obes* 12: 1923–1930. https://doi.org/10.2147/DMSO.S222066
6. Burghen GA, Givens JR, Kitabchi AE (1980) Correlation of hyperandrogenism with hyperinsulinism in polycystic ovarian disease. *J Clin Endocrinol Metab* 50: 113–116. https://doi.org/10.1210/jcem-50-1-113
7. DeFronzo RA, Tobin JD, Andres R (1979) Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237: E214–E223. https://doi.org/10.1152/ajpendo.1979.237.3.E214
8. Chen H, Sullivan G, Quon MJ (2005) Assessing the predictive accuracy of QUICKI as a surrogate index for insulin sensitivity using a calibration model. *Diabetes* 54: 1914–1925. https://doi.org/10.2337/diabetes.54.7.1914

9. Matthews D, Hosker J, Rudenski A, et al. (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28: 412–419. https://doi.org/10.1007/BF00280883
10. Polak K, Czyzyk A, Simoncini T, et al. (2016) New markers of insulin resistance in polycystic ovary syndrome. *J Endocrinol Invest* 40: 1–8. https://doi.org/10.1007/s40618-016-0523-8
11. Parrettini S, Cavallo M, Gaggia F, et al. (2020) Adipokines: a rainbow of proteins with metabolic and endocrine functions. *Protein Pept Lett* 27: 1204–1230. https://doi.org/10.2174/0929866527666200505214555
12. Wu H, Ballantyne C (2020) Metabolic inflammation and insulin resistance in obesity. *Circ Res* 126: 1549–1564. https://doi.org/10.1161/CIRCRESAHA.119.315896
13. Klok M, Jakobsdottir S, Drent M (2007) The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. *Obes Rev* 8: 21–34. https://doi.org/10.1111/j.1467-789X.2006.00270.x
14. Semple R, Cochran E, Soos M, et al. (2008) Plasma adiponectin as a marker of insulin receptor dysfunction: clinical utility in severe insulin resistance. *Diabetes Care* 31: 977–979. https://doi.org/10.2337/dc07-2194
15. Fuke Y, Fujita T, Satomura A, et al. (2010) Alterations of insulin resistance and the serum adiponectin level in patients with type 2 diabetes mellitus under the usual antihypertensive dosage of telmisartan treatment. *Diabetes Technol Ther* 12: 393–398. https://doi.org/10.1089/dia.2009.0126
16. Meilleur K, Doumatey A, Huang H, et al. (2010) Circulating adiponectin is associated with obesity and serum lipids in West Africans. *J Clin Endocrinol Metab* 95: 3517–3521. https://doi.org/10.1210/jc.2009-2765
17. Brabant G, Müller G, Horn R, et al. (2005) Hepatic leptin signaling in obesity. *FASEB J* 19: 1048–1050. https://doi.org/10.1096/fj.04-2846fje
18. Ottawa Hospital Research Institute, The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Canada Ottawa Hospital Research Institute, 2021. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
19. Liu S, Hu W, He Y, et al. (2020) Serum Fetuin—A levels are increased and associated with insulin resistance in women with polycystic ovary syndrome. *BMC Endocr Disord* 20: 67. https://doi.org/10.1186/s12902-020-0538-1
20. Kort D, Kostolias A, Sullivan C, et al. (2015) Chemerin as a marker of body fat and insulin resistance in women with polycystic ovary syndrome. *Gynecol Endocrinol* 31: 152–155. https://doi.org/10.3109/09513590.2014.968547
21. Bannigida D, Nayak S, Vijayaragavan R (2020) Serum visfatin and adiponectin—markers in women with polycystic ovarian syndrome. *Arch Physiol Biochem* 126: 283–286. https://doi.org/10.1080/13813455.2018.1518987
22. Fouani F, Fadaei R, Moradi N, et al. (2020) Circulating levels of Meteorin-like protein in polycystic ovary syndrome: A case-control study. *PLoS One* 15: e0231943. https://doi.org/10.1371/journal.pone.0231943
23. Tang C, Li X, Tang S, et al. (2020) Association between circulating zinc-α2-glycoprotein levels and the different phenotypes of polycystic ovary syndrome. *Endocr J* 67: 249–255. https://doi.org/10.1507/endocrj.EJ18-0506

24. Shin H, Lee D, Lee J (2011) Adiponectin in women with polycystic ovary syndrome. *Korean J Fam Med* 32: 243–248. https://doi.org/10.4082/kjfm.2011.32.4.243
25. Saklayen M (2018) The global epidemic of the metabolic syndrome. *Curr Hypertens Rep* 20: 12. https://doi.org/10.1007/s11906-018-0812-z
26. DerSimonian R, Laird N (2015) Meta-analysis in clinical trials revisited. *Contemp Clin Trials* 45: 139–145. https://doi.org/10.1016/j.cct.2015.09.002
27. Gözüküçük M, Yarcı Gürsoy A, Destegül E, et al. (2020) Adiponectin and leptin levels in normal weight women with polycystic ovary syndrome. *Horm Mol Biol Clin Investig* 41. https://doi.org/10.1515/hmbci-2020-0016
28. Yildizhan R, Ilhan G, Yildizhan B, et al. (2011) Serum retinol-binding protein 4, leptin, and plasma asymmetric dimethylarginine levels in obese and nonobese young women with polycystic ovary syndrome. *Fertil Steril* 96: 246–250. https://doi.org/10.1016/j.fertnstert.2011.04.073
29. Yang S, Wang Q, Huang W, et al. (2016) Are serum chemerin levels different between obese and non-obese polycystic ovary syndrome women?. *Gynecol Endocrinol* 32: 38–41. https://doi.org/10.3109/09513590.2015.1075501
30. El-Gharib MN, Badawy TE (2014) Correlation between insulin, leptin and polycystic ovary syndrome. *J Basic Clin Reprod Sci* 3: 49–53. https://doi.org/10.4103/2278-960X.129281
31. Cankaya S, Demir B, Aksakal SE, et al. (2014) Insulin resistance and its relationship with high molecular weight adiponectin in adolescents with polycystic ovary syndrome and a maternal history of polycystic ovary syndrome. *Fertil Steril* 102: 826–830. https://doi.org/10.1016/j.fertnstert.2014.05.032
32. Sharifi F, Hajihosseini R, Mazloomi S, et al. (2010) Decreased adiponectin levels in polycystic ovary syndrome, independent of body mass index. *Metab Syndr Relat Disord* 8: 47–52. https://doi.org/10.1089/met.2009.0036
33. Li H, Chen Y, Li Y, et al. (2015) A case-control study of correlation between serum adiponectin levels and polycystic ovary syndrome. *Zhonghua Fu Chan Ke Za Zhi* 50: 814–818. (Article in Chinese)
34. Mirza SS, Shafique K, Shaikh AR, et al. (2014) Association between circulating adiponectin levels and polycystic ovarian syndrome. *J Ovarian Res* 7: 18. https://doi.org/10.1186/1757-2215-7-18
35. Jahromi NB, Dabaghmanesh MH, Parsanezhad ME, et al. (2017) Association of leptin and insulin resistance in PCOS: A case-controlled study. *Int J Reprod Biomed* 15: 423–428.
36. Baig M, Rehman R, Tariq S, et al. (2014) Serum leptin levels in polycystic ovary syndrome and its relationship with metabolic and hormonal profile in Pakistani females. *Int J Endocrinol* 2014: 132908. https://doi.org/10.1155/2014/132908
37. Gowthami P, Kiranmayi V, Rani BS, et al. (2019) Study of serum adiponectin levels in women with polycystic ovary syndrome. *Indian J Obstet Gynecol Res* 6: 288–292.
38. Barrea L, Arnone A, Annunziata G, et al. (2019) Adherence to the Mediterranean diet, dietary patterns and body composition in women with polycystic ovary syndrome (PCOS). *Nutrients* 11: 2278. https://doi.org/10.3390/nu11102278