Article

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Risk Correlation Analysis between Polycystic Ovary Syndrome (PCOS) and Serum Visfatin Levels in Middle-Aged Women: Systematic Review and Meta-Analysis

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Background: Polycystic ovary syndrome (PCOS) is an endocrine disorder that occurs frequently in women of childbearing age and is associated with insulin resistance. Serum visfatin can affect insulin resistance by binding to insulin receptors and further affect the occurrence and development of PCOS. In this study, we investigated the current status of serum visfatin levels in patients with PCOS through a literature search and meta-analysis.

Methods: We searched online Pubmed, Embase, Web of Science, the Cochrane Library, CNKI (China National Knowledge Infrastructure), CBMdisc (China Biology Medicine disc) databases and registered websites such as the ICTRP (International Clinical Trial Registration Platform) and clinicaltrials.gov (https://clinicaltrials.gov/) for case-control studies on PCOS and visfatin levels, assessed the quality of the included articles with the Newcastle-Ottawa Scale (NOS scale), and combined the comparison of serum visfatin levels between patients with PCOS and healthy individuals from high-quality studies.

Results: 20 research papers were included in the quantitative analysis of this study. The combined analysis showed that obese patients with PCOS had statistically significantly higher visfatin levels than healthy people [MD (mean difference) = 12.94, 95% CI (confidence interval) (6.52–19.37), Z = 3.95, $p < 0.0001$]. Visfatin levels were higher in non-obese patients with PCOS than in healthy people and are statistically significant [MD = 14.98, 95% CI (5.80–24.16), Z = 3.20, $p = 0.001$]. Heterogeneity in the combined analysis was not related to study location, the publication year of the literature, source of serum samples, but was influenced by the quality of the literature. After excluding the most influential papers, the combined analysis was conducted again, and the conclusion was consistent with that before the exclusion. The results of Egger's test showed no significant publication bias.

Conclusions: High serum visfatin levels are a natural feature of PCOS and are not associated with obesity; Serum visfatin levels may be a potential marker for the diagnosis of PCOS, but their relationship with PCOS and insulin resistance remains worthy of in-depth investigation.

Keywords: polycystic ovary syndrome (PCOS); serum visfatin; correlation analysis

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder that occurs frequently in women of reproductive age and is mainly characterized by hyperandrogenism and persistent anovulation, with an incidence as high as 5%–10% [1]. If patients are not intervened on time, it can lead to abnormal ovulation function, and even cause infertility, seriously affecting women's physical and mental health and family stability [2]. Therefore, it is important to investigate the pathogenesis of PCOS and give targeted treatment to control the progression of the disease and improve the quality of life of patients. Some studies have shown that insulin resistance caused by hormone secretion disorders *in vivo* is closely related to the occurrence and development of PCOS [3], which is one of the main pathophysiological characteristics of PCOS. Other studies have shown that insulin resistance is present in about 50%–70% of patients with PCOS, and insulin resistance is a chronic subclinical inflammatory process, and inflammatory or proinflammatory factors play an important role in the development and progression of insulin resistance [4]. Visfatin is a recently discovered adipocytokine that is specifically and highly expressed in visceral fat and is associated with obesity, and its

serum levels are affected by a variety of hormones and inflammatory cytokines and is positively correlated with visceral fat mass, which can bind insulin receptors, activate mitogen-activated protein kinase signaling pathways and increase insulin resistance [5,6]. However, serum visfatin levels in patients with PCOS reported in several studies presented differences, and the results were conflicting. In a study by Garruti G *et al.* [7], visfatin levels were not significantly different in patients with PCOS compared with healthy people. A single study could not feedback on the overall study results, therefore, we performed this meta-analysis to resolve the conflicts between different study results on the same topic.

Materials and Methods

Database and Search Strategy

We searched in the online database Pubmed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com), Web of Science (https://www.webofscience.com), the Cochrane Library (https://www.cochranelibrary.com), CNKI (China National Knowledge Infrastructure) (https://cnki.net), CBMdisc (China Biology Medicine disc) (http://www.sinomed.ac.cn) for articles related to polycystic ovary syndrome, and we also searched the registered but unpublished literature in ICTRP (International Clinical Trial Registration Platform) (https://www.who.int/clinical-trials-registry-platform) and clinicaltrials.gov (https://clinicaltrials.gov/). We only included papers published in the recent 22 years, electronic search with keyword combination "visfatin" and "polycystic ovarian syndrome" from January 2000 to April 2022, and we set the screening criteria to screen the retrieved literature. The search query sequence used in Pubmed is the following: Query (polycystic ovarian syndrome [Title/Abstract] or PCOS [Title/Abstract] or Stein-Leventhal Syndrome [Title/Abstract] or Sclerocystic Ovarian Degeneration [Title/Abstract] or Sclerocystic Ovary Syndrome [Title/Abstract] or Polycystic Ovarian Syndrome [Title/Abstract] or Sclerocystic Ovaries [Title/Abstract] or Sclerocystic Ovary [Title/Abstract] and visfatin [Title/Abstract]) (Pubmed).

Literature Inclusion Criteria

① Type of study: All literature was case-control studies; ② Study subjects: The subjects in the case group were all women aged over 18 years who were diagnosed with PCOS, with symptoms of anovulation, oligovulation, hyperandrogenism, and polycystic ovarian changes on ultrasound imaging, and the diagnosis for PCOS was based on the 2003 Rotterdam consensus meeting guideline [8]; The subjects in the control group were healthy people. ③ Investigation process: In all subjects, cubital venous blood was collected in the morning under fasting state on days 3–5 of the menstrual cycle (no dominant follicle was monitored by B ultrasound in amenorrhea patients), and serum (or plasma) visfatin levels were measured by enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay (RIA). ④ Outcome indicators: Multiple indicators other than visfatin were included in the study, such as total cholesterol (TC), low-density lipoprotein (LDL), and C-Reactive Protein (CRP), but we only obtained the data of visfatin, which are expressed in the form of mean + standard deviation (SD), the unit is ng/mL, and other data not in ng/mL are converted to this unit, such as the conversion formula of ng/mL and nmol/L is: 1 ng/mL = 3.467 nmol/L. The data reported in $\log_2$ (visfatin levels) in a few publications were converted to decimal data to minimize

Literature Exclusion Criteria

① We excluded all studies other than case control, such as randomized controlled trials (RCT), cohort studies (retrospective or prospective), case series, individual studies, conference notes, and reviews. ② Adolescent patients with PCOS that were <18 years old were excluded; ③ Studies lacking outcome indicators, or having no data were also excluded; As well as ④ studies of low quality; ⑤ And PCOS patients who were receiving treatment or have undergone any intervention.

Literature Screening

After retrieval, import into the software "NoteExpress V3.0.2" (Released by AEGEANSOFTWARE, Beijing, China) for unified management was conducted, and the de-duplication function of the software to exclude repeated literature was used. For the remaining literature, the abstracts were read to remove repeated concepts. If two papers reported the same study, the one with the most robust data was retained. According to the pre-set inclusion and exclusion criteria, two investigators read the title and abstract for further screening, cross-checked and discussed the screening results to determine the selected literature. The full text of all the primary selected literature was obtained. If the original text could not be obtained from the Internet, the author of the original text was contacted by phone or email. If the original text could not be obtained, that literature was excluded. The full text of the publications was read and the data were extracted. If there was no available data (or data index) in the literature it was excluded.

Literature Quality Evaluation and Risk of Bias Assessment

The Newcastle-Ottawa Scale (NOS scale) [9] was used to analyze the quality of the included literature. The scale was used to evaluate the object selection, comparability and outcome indicators of the literature. The maximum score was 9 points, and a score of more than 5 points was considered good quality. Higher scores indicate better literature quality and less bias, with scores of 5–7 being of moderate quality and 8–9 being of high quality. Articles with scores under 5 were excluded.

Data Extraction

Two researchers independently extracted data from the literature: Study type, publication year and month of the literature, study location, patient age, height, weight, body mass index (BMI), serum test method, and visfatin data. After data extraction was completed by two researchers, each other's results were cross-checked and discrepancies were discussed and finalized.

Statistical Methods

(a) Differences in visfatin levels between patients with PCOS and healthy people were reported using mean difference (MD) and 95% CI (confidence interval), and the combined effect size results were presented in forest plots. (b) The heterogeneity of literature was analyzed using I^2 analysis and Q test, and heterogeneity sex was expressed in the results using I^2 >50% or $p < 0.1$. (c) For articles with statistically significant heterogeneity, the random effects model was used for combined analysis, and the inverse variance model and Cohen's statistical method were also used. Otherwise, the fixed effect size was used and calculated by the inverse variance model and Cohen's statistical method. (d) A subgroup analysis was used to investigate the source of heterogeneity. (e) The influential diagnosis was performed on the analysis results to find out the literature with the greatest impact on the results. (f) The Egger's test was used to quantitatively detect publication bias and the *p*-Curve plot was used to present publication bias [10]. (g) Two-sided $p < 0.05$ was considered statistically significant for the above analyses.

Results

Literature Screening Process and Results

The flow chart of the literature selection is shown in Fig. 1. 447 articles were initially retrieved, 426 articles were retrieved in the database, 21 articles were retrieved from the registered website, 140 articles were removed after repeatability testing, 105 articles were preliminarily screened and removed, 45 articles that could not be obtained full text were removed, and 137 articles were included in the final analysis. After reading the full text, articles with low quality, no data or outcome indicators were removed, and finally, 20 articles [5,11–29] were included in the quantitative analysis. A total of 1913 patients were included in the final statistics.

In one of the articles [30], the subjects were adolescents with PCOS, so they were excluded. In other papers [31,32], patients with PCOS received manual intervention, so they were also excluded. In another article [33], no healthy population served as the control group, so they were excluded; And in another study [34], due to low quality, there may be a large bias. We did not list all the excluded articles.

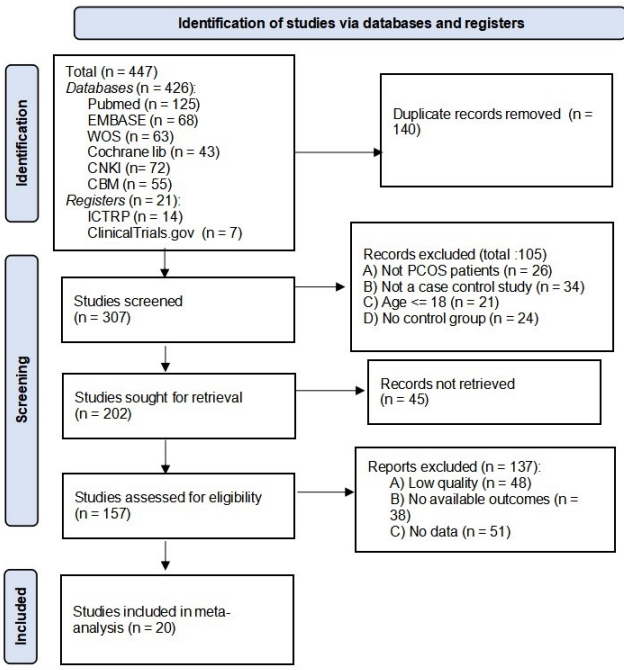

Fig. 1. Literature selection flow chart. 447 literatures were identified as initial studies, 307 were screened and 20 included in meta-analysis.

Basic Characteristics of the Selected Literature

20 articles were included in this study, all of which were case-control studies; There were 1032 cases (53.9%) in the observation group (PCOS) and 881 cases (46.1%) in the control group. There are two sources of samples: Serum and plasma; The detection method is ELISA or RIA (Table 1, Ref. [5,11–29]).

Literature Quality and Bias Evaluation

Among all the 20 included articles, the quality score of the articles [5,11–18,25,26,29] with less bias and high quality was 8–9 points. The score of articles [19–24,27,28] with a small amount of bias and moderate quality was 5–7 points. The number of studies with high quality was 12 (60%) and the number of articles with moderate quality was 8 (40%) (Table 2, Ref. [5,11–29]).

Visfatin Levels in Obese Women with PCOS Compared with the Control Group

A total of 11 articles [5,11,12,15,18,19,22,23,25,27,29] reported the comparison of visfatin levels between obese patients with PCOS and healthy people, with literature heterogeneity ($I^2 = 99\%$, $p < 0.001$). Using the random effect mode and meta-analysis showed that visfatin levels were statistically significantly higher in obese patients with PCOS than in healthy people [MD = 12.94, 95% CI (6.52–19.37), Z = 3.95, $p < 0.0001$] (Fig. 2).

Table 1. Basic characteristics of the included literature.

Author and publication date	Region	Sample source	Test method	Age	Obese	PCOS		Control		Quality grade
						Sample number	Visfatin (ng/mL)	Sample number	Visfatin (ng/mL)	
Bannigida DM [5] 2020	India	Serum	ELISA	24.3 ± 4.3	Y	50	22.99 ± 1.39	50	6.91 ± 1.11	High
					N	50	13.93 ± 1.21	50	7.19 ± 1.13	
Dıkmen E [11] 2011	Turkey	Plasma	ELISA	23.7 ± 6.1	Y	25	100.5 ± 94.7	20	27.2 ± 14.9	High
					N	17	37.5 ± 21.9	17	29.2 ± 15.6	
Olszanecka-Glinianowicz M [12] 2012	Poland	Serum	ELISA	24.8 ± 4.8	Y	44	8.9 ± 4.7	36	7.5 ± 2.5	High
					N	39	9.1 ± 3.0	31	10.5 ± 10.6	
Panidis D [13] 2008	Greece	Plasma	ELISA	23.7 ± 0.95	N	25	73.35 ± 11.54	24	15.17 ± 2.03	High
Kim JJ [14] 2018	Korea	Serum	ELISA	23.8 ± 5.5	N	74	3.41 ± 1.41	74	3.28 ± 1.01	High
Farshchian F [15] 2014	Iran	Serum	ELISA	34.2 ± 6.8	Y	24	3.46 ± 1.24	24	3.49 ± 1.49	High
					N	16	3.16 ± 0.93	16	3.15 ± 1.06	
Jongwutiwes T [16] 2009	Tailand	Serum	ELISA	32.77 ± 4.36	N	40	100.39 ± 41.90	40	45.09 ± 28.24	High
Chan TF [17] 2007	China	Plasma	ELISA	24.6 ± 4.6	N	26	336.8 ± 50.2	26	282.4 ± 43.3	High
Abdul-Maksoud RS [18] 2020	Egypt	Serum	ELISA	33.5 ± 5.41	Y	70	42.10 ± 14.03	35	20.14 ± 8.71	High
					N	70	39.00 ± 13.01	35	18.21 ± 6.07	
Wang Y [19] 2020	China	Serum	ELISA	25.5 ± 3.3	Y	73	95.3 ± 31.9	75	73.2 ± 20.3	Mid
Wang JM [20] 2018	China	Serum	ELISA	25.2 ± 4.79	N	60	50.8 ± 5.58	60	36.2 ± 4.12	Mid
Dambala K [21] 2017	Korea	Plasma	ELISA	29.0 ± 5.7	N	42	3.51 ± 2.29	40	2.38 ± 2.00	Mid
Tan BK [22] 2006	UK	Plasma	ELISA	29.3 ± 1.8	Y	8	30.2 ± 10.4	8	11.2 ± 6.2	Mid
Gul OO [23] 2015	Turkey	Serum	ELISA	27.5 ± 5.7	Y	18	67.1 ± 18.8	18	62.7 ± 18.4	Mid
					N	19	76.7 ± 32.4	18	62.7 ± 18.4	
Cassar S [24] 2015	Japan	Serum	ELISA	28 ± 6	Y	22	81 ± 30	18	83 ± 33	Mid
					N	22	70 ± 16	22	75 ± 15	
Yildiz BO [25] 2010	Turkey	Plasma	ELISA	25.4 ± 4.4	N	27	37.9 ± 18.2	19	19.8 ± 17.5	High
Gen R [26] 2009	Turkey	Plasma	ELISA	23.46 ± 5.15	N	21	30.9 ± 1.5	15	20.4 ± 1.41	High
Kowalska I [27] 2007	Poland	Serum	RIA	26.24 ± 6.00	Y	47	67.14 ± 36.99	20	53.56 ± 32.48	Mid
Güdücü N [28] 2012	Turkey	Plasma	ELISA	24.67 ± 4.38	N	37	42.76 ± 3.27	30	42.60 ± 1.78	Mid
Zhang XF [29] 2015	China	Serum	ELISA	28.41 ± 2.90	Y	33	50.1 ± 5.94	30	36.17 ± 4.15	High
					N	33	52.5 ± 6.54	30	36.17 ± 4.15	

Abbreviations: ELISA, enzyme-linked immunosorbent assay; RIA, radiation immunity analysis; Y, yes; N, no.

Table 2. Quality assessment based on the Newcastle-Ottawa Scale (NOS).

Study	Case selection (4)	Comparability (2)	Outcome indicators (3)	Total (9)
Bannigida DM [5] 2020	4	2	3	9
Dıkmen E [11] 2011	4	2	2	8
Olszanecka-Glinianowicz M [12] 2012	4	2	2	8
Panidis D [13] 2008	4	2	3	9
Kim JJ [14] 2018	4	2	2	8
Farshchian F [15] 2014	4	2	2	8
Jongwutiwes T [16] 2009	4	2	3	9
Chan TF [17] 2007	4	2	2	8
Abdul-Maksoud RS [18] 2020	4	2	3	9
Wang Y [19] 2020	1	2	2	5
Wang JM [20] 2018	1	2	2	5
Dambala K [21] 2017	2	2	2	6
Tan BK [22] 2006	2	2	2	6
Gul OO [23] 2015	3	2	2	7
Cassar S [24] 2015	2	2	2	6
Yildiz BO [25] 2010	4	2	2	8
Gen R [26] 2009	4	2	2	8
Kowalska I [27] 2007	2	2	2	6
GüdücüN [28] 2012	2	2	2	6
Zhang XF [29] 2015	4	2	2	8

Visfatin Levels in Non-Obese Women with PCOS Compared with the Control Group

A total of 17 articles [5,11–18,20,21,23–26,28,29] reported the comparison of visfatin levels between non-obese patients with PCOS and healthy people, with literature heterogeneity (I^2 = 99%, $p < 0.001$), using the random effect mode and meta-analysis showed that visfatin levels were statistically significantly higher in non-obese patients with PCOS than in healthy people [MD = 14.98, 95% CI (5.80–24.16), Z = 3.20, $p = 0.001$] (Fig. 3).

Subgroup Analysis

In a combined analysis of visfatin levels in non-obese patients with PCOS compared with healthy people, to investigate the source of heterogeneity, a subgroup analysis was performed using the source of serum samples, and heterogeneity remained within the two groups (I^2 = 99%), with no significant difference in heterogeneity between groups (p = 0.37). It indicated that serum samples were not a source of heterogeneity (Fig. 4).

A subgroup analysis was performed sequentially according to the study site, publication year, and quality of the literature, and the p values of heterogeneity between groups were (0.36, 0.259, 0.038), the p value of "quality of the literature" was < 0.05, which was statistically significant, therefore, "quality of the literature" was one of the sources of heterogeneity in this analysis (Table 3).

Influence Analysis

In the combined analysis of visfatin levels in non-obese patients with PCOS compared with healthy people, an influence analysis was performed (Fig. 5). Panidis D *et al.* [13] contributed the most to heterogeneity, while Kim JJ *et al.* [14] contributed the most to the results. Excluding these two studies, the remaining 15 articles were recombined and analyzed, resulting in the following effect size: [MD = 12.43, 95% CI (4.77–20.09), Z = 3.18, $p = 0.001$].

Publication Bias Analysis

In the combined analysis of visfatin levels in non-obese patients with PCOS compared with healthy people, publication bias was tested using Egger's test (p = 0.07), suggesting that there may be a small publication bias, as shown in Table 4. When the p-curve presentation was used, a total of 10 articles (58.8%) were statistically significant, as shown in Fig. 6.

Discussion

PCOS is a syndrome characterized by oligomenorrhea, polycystic ovarian enlargement, chronic anovulation, infertility, and amenorrhea, which not only triggers reproductive dysfunction but also increases the risk of diabetes from cardiovascular disease [30,31]. Insulin resistance is an important component of PCOS, and studies have shown that up to 50% of PCOS patients have varying degrees of insulin resistance [18]. Insulin resistance can lead to glucose utilization and metabolic disorders in fat, skeletal muscle and other tissues, exacerbate oxidative stress, and promote the formation of high-grade glycation end products, resulting in impaired vascular endothelial function. At the same time, insulin resistance increases free fatty acid levels, leads

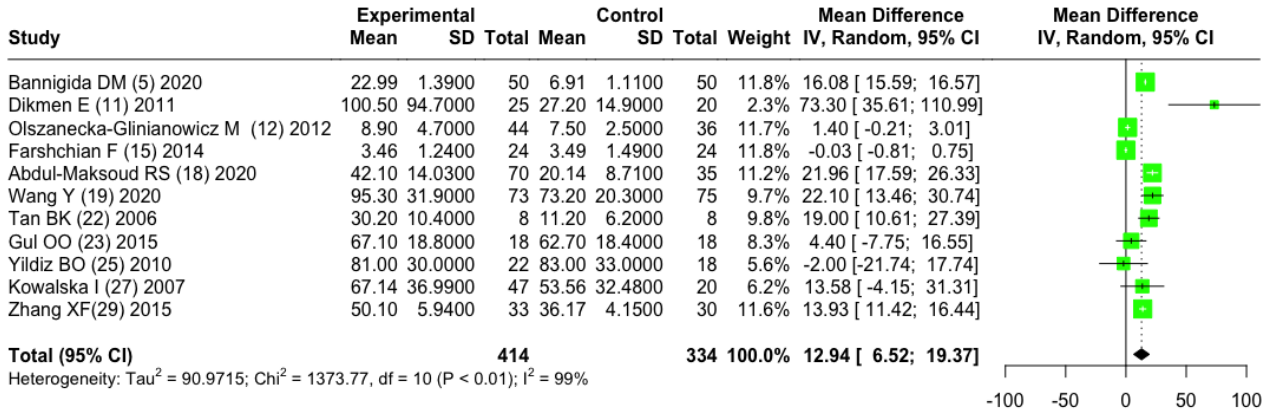

Fig. 2. Plot of visfatin levels in obese women with PCOS compared with the control group. Green box represents the MD and 95% CI for each study; Black diamond represents the total MD and 95% CI; MD, mean difference; SD, standard deviation; IV, inverse variance; CI, confidential interval.

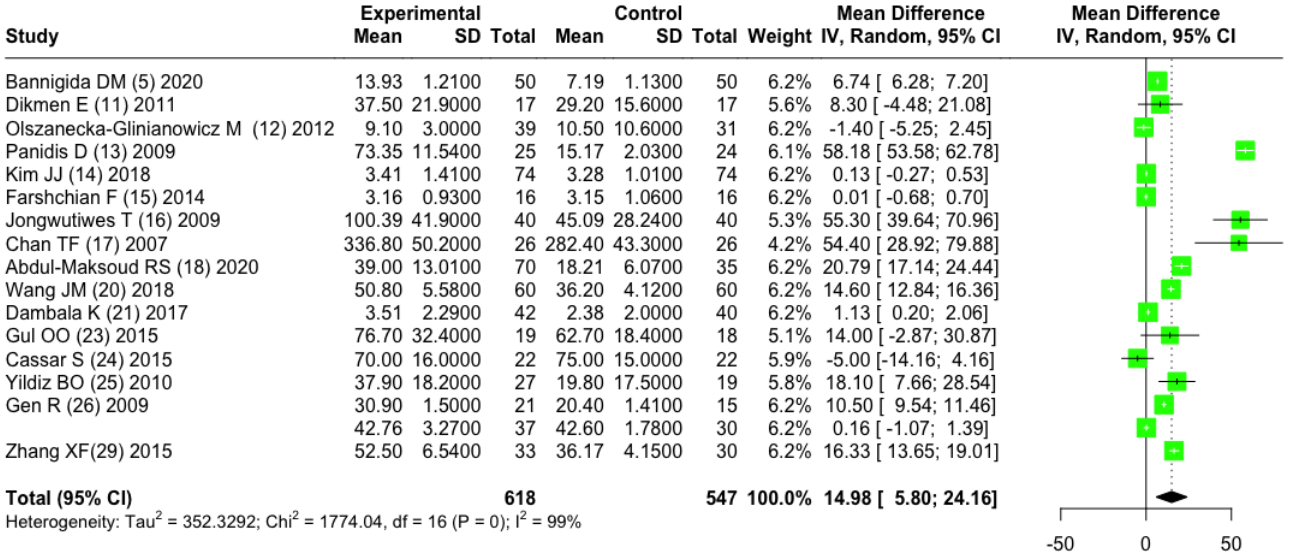

Fig. 3. Plot of visfatin levels in non-obese women with PCOS compared with the control group. Green box represents the MD and 95% CI for each study; Black diamond represents the total MD and 95% CI; MD, mean difference; SD, standard deviation; IV, inverse variance; CI, confidential interval.

to lipid metabolism disorders, increases serum levels of inflammatory factors, and promotes PCOS disease progression [21,23].

Visfatin is an adipokine found in 2005 to be closely related to glucose and lipid metabolism, secreted by visceral adipocytes, and its cDNA (complementary deoxyribonucleic acid) coding sequence is highly conserved in evolution, homologous to pre-B cell colony-enhancing factors, and has many different biological activities: (a) It can induce the expression of inflammatory cytokines such as IL (interleukin)-6 and promote the body in a low-grade chronic inflammatory state; (b) It interacts with insulin receptors and shows anti-insulin or insulin-like effects in the cytoplasm and can reduce blood glucose levels; (c) It can catalyze nicotinamide adenine dinucleotide biosynthesis [35,36]. Serum correlates are closely related to BMI and can influence insulin resistance [37].

In this meta-analysis, we identified 20 relevant articles by electronic search, involving 1913 patients and including 1032 cases (53.9%) in the observation group (PCOS) and 881 cases (46.1%) in the control group. We divided the study into two groups, namely obese women *vs* non-obese women, and the results of both groups showed that visfatin levels in serum (or plasma) of patients with PCOS were significantly higher than those of healthy people, which showed that visfatin levels in serum of patients with PCOS

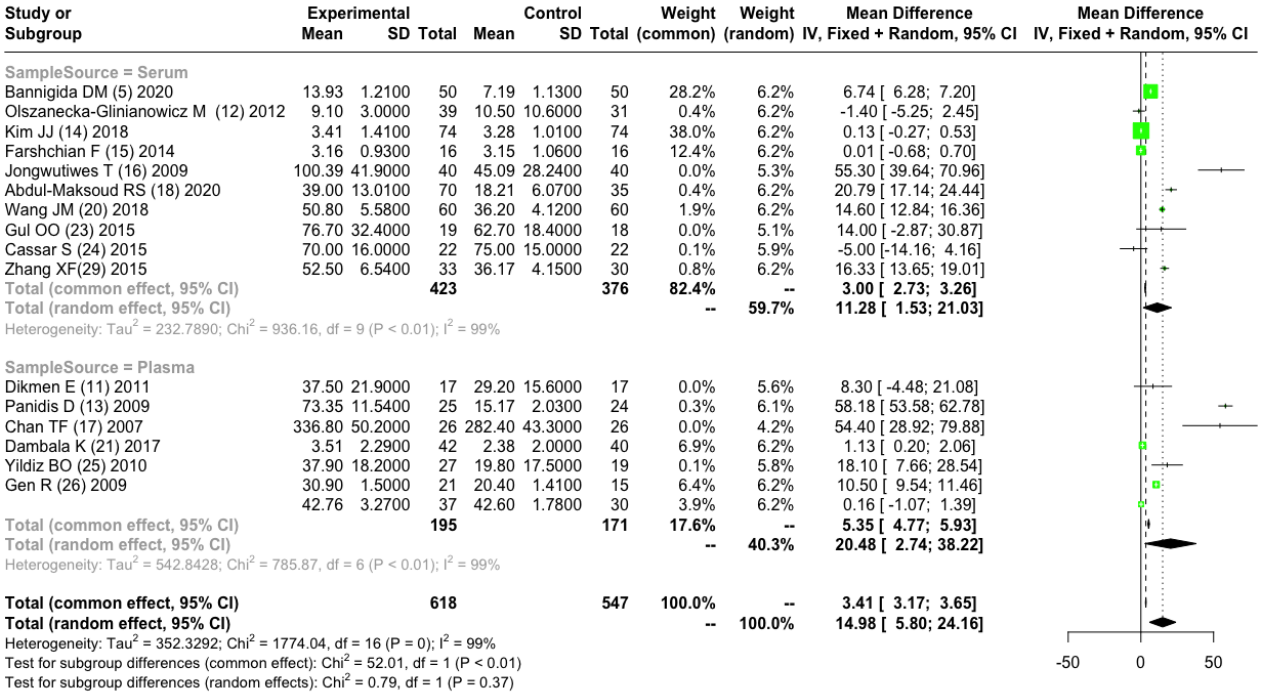

Fig. 4. Comparison of visfatin levels between non-obese patients with PCOS and healthy people (grouped by serum sample source). MD, mean difference; SD, standard deviation; IV, inverse variance; Green box represents the MD and 95% CI for each study; Black diamond represents the total MD and 95% CI.

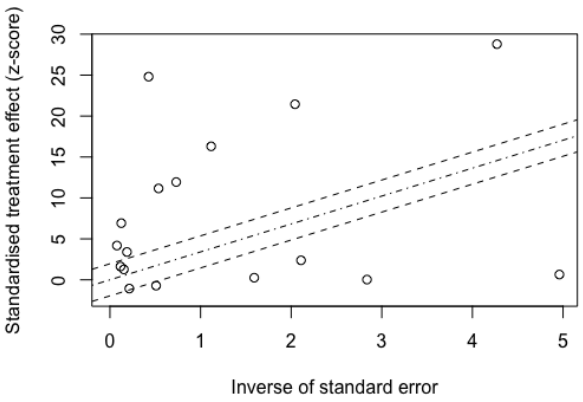

Fig. 5. The radial plot of influence analysis.

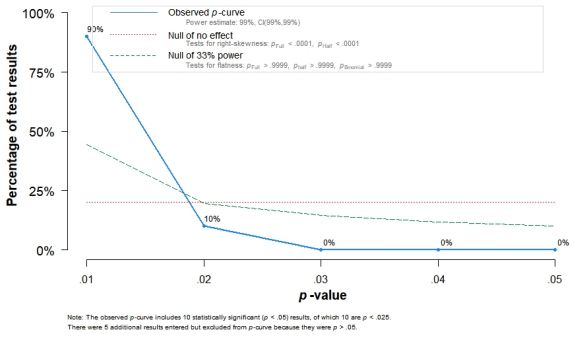

Fig. 6. The plot of *p*-curve analysis.

were higher than those of healthy people, regardless of obesity. This result suggests that high serum visfatin levels are a natural feature of polycystic ovary syndrome, suggesting that visfatin may be a potential biomarker for polycystic ovary syndrome. A study showed that visfatin was significantly positively correlated with TC and LDL, suggesting that visfatin is closely related to lipid metabolism in patients with PCOS [29]. TC synthesis is increased in patients with PCOS, which inhibits LDL receptor activity, indirectly inhibits the normal degradation process of LDL, and increases LDL levels in plasma, leading to atherosclerosis. Another study states that overexpression or reduction of visfatin can have deleterious effects on the body [19].

Sun Y *et al.* [38] also included 20 articles for combined analysis in a 2015 meta-analysis, but several on-treatment PCOS articles were included in this meta-analysis, which led to a large bias in the analysis process. In this study, the subjects included in the literature were strictly selected as untreated patients with PCOS. All the articles had NOS scores of more than 5 points, good quality and more true and credible results. However, this study only judged the serum levels of visfatin and failed to investigate the correlation between visfatin and insulin resistance, which is a shortcoming of this study.

Table 3. Subgroup analysis of visfatin levels in patients with PCOS compared with healthy people.

Grouping method	Subgroup	Literature number	MD, 95% CI	Heterogeneity		Heterogeneity test *p*-value
				I^2	*p*	
Study region	Asia	7	19.6291 [3.2198–36.0385]	99.1%	< 0.001	0.36
	Europe	9	11.1842 [–1.5020–23.8703]	99.1%	< 0.001	
	Africa	1	20.7900 [17.1386–24.4414]	-	-	
Publication year	<year 2000	4	43.6152 [19.6944–67.5359]	98.7%	< 0.001	0.259
	≥year 2000	13	6.8134 [2.0561–11.5708]	99.3%	< 0.001	
Quality	High	12	19.4996 [7.3051–31.6941]	98.1%	< 0.001	0.038
	Mid	5	4.4001 [–3.0355–11.8357]	99.3%	< 0.001	
Sample source	Serum	10	11.2793 [1.5330–21.0255]	99.0%	< 0.001	0.37
	Plasma	7	20.4812 [2.7444–38.2180]	99.2%	< 0.001	

Table 4. Egger's test publication bias analysis report.

Test method	Intercept	Confidence interval	*t*	*p*
Egger's test	6.132	–0.04, –12.31	1.95	0.07

Polycystic ovary syndrome is usually treated with drugs that reduce serum androgen levels, induce ovulation and improve insulin resistance. A study by Jin Z *et al.* [39] showed that a class of tanshinone drugs extracted from natural Salvia miltiorrhiza has strong anti-inflammatory, bacteriostatic and metabolic regulation functions, and promotes body metabolism by improving body microcirculation. Clinically, they are mostly used to regulate glucose metabolism and lipid metabolism in patients with diabetes, but they can also be used to treat PCOS by regulating the hypothalamus pituitary adrenal axis.

In this study, the results among different articles showed statistically significant heterogeneity when combined. Through the discussion of heterogeneity, we learned that the study site, publication year and source of serum samples were not the causes of heterogeneity, but the quality of the literature was one of the causes of heterogeneity. The effect size MD obtained by high-quality articles with low risk of bias was larger (19.5 ng/mL *vs* 4.4 ng/mL), suggesting that we should try to include high-quality articles to reduce the heterogeneity of literature combined.

In the influence analysis, we diagnosed those two articles [13,14] were the two most influential articles on heterogeneity and outcome, and excluding these two studies, the resulting pooled effect size MD did not change the previous conclusion, which shows that our conclusion is stable.

In the analysis of publication bias, the Egger's test showed that there may be some publication bias, but it was not statistically significant, and the *p*-Curve also showed that 58.8% of the literature was within the valid range, which reflected the credibility of our conclusions.

Conclusions

The results of this study showed that high serum visfatin levels are a natural feature of polycystic ovary syndrome, regardless of whether the patient is obese or not. Serum visfatin levels may be a potential marker for the diagnosis of polycystic ovary syndrome, but its relationship with PCOS and insulin resistance remains worthy of in-depth investigation.

Availability of Data and Materials

Not applicable.

Author Contributions

JC, LMH and MNS—designed the research study; YCL, YHX and XY—performed the research; YCL, YHX and LPM—analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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