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Meta-Analysis

Impact of metformin therapy on serum visfatin levels in polycystic ovary syndrome: a systematic review and randomized permuted meta-analysis

E. Prabhakar Reddy[1], Hemanth Raj Thangappazham[2], Nabnita Patnaik[3], Pragathi Duggina[4], Kuladeep L Kumar[5], Saurabh Varshney[6], Ashoo Grover[7], Pratima Gupta[8], Kumar Guru Mishra[9], Seshadri Reddy Varikasuvu[10]*

[1] CEO & Professor of Biochemistry, Anna Gowri Medical College and Hospital, Parameswaramangalam, Puttur, Tirupati District, Andhra Pradesh, India.
[2] Institute for Regenerative Medicine, Wake Forest University, Winston-Salem, USA
[3] Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences (AIIMS), Bibinagar, India
[4] Scientific officer, Sri Padmavati Mahila Visvavidyalayam, Tirupati, India
[5] Mohan Babu University, Tirupati, India
[6] Executive Director and CEO, All India Institute of Medical Sciences (AIIMS), Deoghar, India
[7] Scientist-G & Head, Delivery Research Division, The Indian Council of Medical Research (ICMR), New Delhi, India
[8] Department of Microbiology, All India Institute of Medical Sciences (AIIMS), Deoghar, India
[9] Department of Community Medicine, Apollo Institute of Medical Sciences and Research, Hyderabad, India
[10] Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), Deoghar, India

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Abstract

Visfatin, an, is associated with reproductive and metabolic disorders like polycystic ovary syndrome (PCOS). Although visfatin levels are known to be elevated in PCOS, the effect of metformin treatment on these levels remains unclear. This meta-analysis aimed to assess changes in circulating visfatin levels before and after metformin intervention in PCOS patients. Relevant studies were identified through comprehensive searches, and a random-effects meta-analysis was conducted to calculate standardized mean differences (SMDs) with 95% confidence intervals (CIs). Sensitivity analysis and randomized permuted meta-analyses (with 1,000, 10,000, and 100,000 iterations) were performed to validate the findings. The analysis included four studies and showed a significant reduction in visfatin levels following metformin treatment (SMD: -0.45, 95% CI: -0.76 to -0.14, p = 0.0043). These results highlight metformin's impact on visfatin levels in PCOS, though larger trials are needed to further explore visfatin's role as a therapeutic target in PCOS.

Keywords: Visfatin, Adipocytokine, Metformin, Meta-analysis, Polycystic ovary syndrome.

1. Introduction

Polycystic ovary syndrome (PCOS) affects 6–10% of women of reproductive age and is a leading cause of female infertility. It is characterized by ovarian dysfunction, hyperandrogenism, and menstrual irregularity, and often includes overweight or obesity along with hyperinsulinemia and insulin resistance (IR) in 50–70% of cases [1]. Adipose tissue contributes to hyperinsulinemia and IR, which are strongly linked to hyperandrogenism in PCOS [2,3]. Metformin, a common insulin sensitizer, can improve metabolic signs and clinical symptoms of PCOS by addressing this pathophysiological link. Its use is associated with benefits such as weight reduction, lowered insulin levels and IR, and improvements in reproductive health including reduced androgen levels, restored menstrual cyclicity, and increased ovulation [4].

Recent studies have demonstrated that several adipocytokines are extensively implicated in the pathophysiological processes of metabolic disorders such as diabetes, obesity, IR, and PCOS [5,6]. Visfatin, a novel adipocytokine, is secreted by various tissues including adipose tissue, hepatocytes, lymphocytes, bone marrow, liver, skeletal muscles, trophoblasts, and immune cells. It acts as an insulin-mimetic adipokine, binding to insulin receptors

* Corresponding author.
E-mail address: lifeschemistry@live.com (S. R. Varikasuvu).
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to enhance glucose uptake in muscle cells and adipocytes and inhibit glucose release from liver cells. Additionally, it displays structurally identity to a cytokine, the pre-B cell colony enhancing factor (PBEF) and exhibits immune-modulatory and proinflammatory properties [7,8].

Evidence indicates that visfatin expression is elevated in PCOS, suggesting its potential as a therapeutic target [9,10]. Studies and recent meta-analyses have consistently shown significant changes in circulatory visfatin levels in PCOS patients compared to controls [11,12]. However, there remains inconclusive evidence regarding the impact of metformin treatment on visfatin levels in PCOS [13]. Thus, this study aimed to conduct a systematic review and meta-analysis to investigate the effect of metformin intervention on circulating visfatin levels in PCOS patients. We further conducted the randomized permuted meta-analysis with bootstrapping approach to obtain a robust and more precise outcome.

2. Materials and methods

2.1. Literature search

To identify relevant studies, we primarily utilized PubMed/MEDLINE and other databases such as the Cochrane Library, Scopus, ScienceDirect, clinical trial registries, and Google Scholar, up until June 23, 2024. The search strategy included both general keywords and Medical Subject Headings (MeSH), with no restrictions on language. Key terms used in the search included "polycystic ovary syndrome" or "PCOS," "visfatin," and "metformin," which were combined using Boolean operators. Furthermore, we manually reviewed the reference lists of pertinent articles to discover any additional studies.

2.2. Criteria and data extraction

The meta-analysis was conducted in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [14], and was prospectively registered with PROSPERO (CRD42024561051). The inclusion criteria for studies were as follows: (1) diagnosis of polycystic ovary syndrome (PCOS) according to the ESHRE/ASRM (Rotterdam) criteria [15]; (2) evaluation of the impact of metformin on circulating visfatin levels; (3) comparison of visfatin levels before and after metformin treatment, including metrics such as mean, standard deviation, interquartile ranges, and mean or median differences; (4) study design could be either randomized or non-randomized; (5) in randomized clinical trials, comparison of visfatin levels between metformin and placebo/comparator groups. Exclusion criteria encompassed duplicate studies, research involving conditions other than PCOS, interventions other than metformin, outcomes other than visfatin, as well as reviews, letters, commentaries, and studies conducted on animals or in cell cultures. Data extracted from the selected studies included authorship, country of origin, study design, diagnostic criteria for PCOS, sample sizes, dosage and duration of metformin treatment, pre-and post-treatment visfatin levels, and any reported adverse events.

2.3. Quality assessment and quantitative analysis

The quality of the studies included in the meta-analysis was evaluated using the Newcastle–Ottawa Scale (NOS), which examines three key domains: selection, comparability, and outcome. The NOS assigns a maximum of three points for the selection domain and two points each for comparability and outcome. Studies that scored between 6 and 7 points were categorized as having good to high quality. The literature search, abstract and full-text screening, data extraction, and quality assessment were performed independently by two authors. Discrepancies were addressed through discussion, and when necessary, the corresponding authors of the studies were contacted via email to obtain additional information or clarification.

2.4. Statistical analysis

The analysis employed the standardized mean difference (SMD) with 95% confidence intervals (CIs) to evaluate changes in visfatin levels before and after metformin treatment in patients with PCOS, utilizing a random-effects model. Heterogeneity was quantified using the DerSimonian-Laird method, with the Q-test and I^2 statistic reported to gauge variability across studies. When heterogeneity was present ($tau^2 > 0$), a prediction interval for the true effect sizes was calculated. Outliers and influential studies were detected through studentized residuals and Cook's distances. To assess publication bias, funnel plot asymmetry was examined using rank correlation and regression tests. Sensitivity analyses, where each study was individually excluded, were performed to test the stability of the findings. Statistical significance was set at a p-value < 0.05. All statistical computations were carried out using Review Manager (version 5.4), Jamovi (version 2.3), OpenMeta (Analyst), and OpenMEE software for randomized permuted analyses. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system was used for evaluating the certainty of evidence. It assesses the quality of evidence across multiple domains such as, risk of bias, inconsistency, indirectness and imprecision of evidence, and other considerations. The GRADE system categorizes the certainty of evidence into four levels: high, moderate, low, and very low.

3. Results

3.1. Search results and study characteristics

Initially, 83 studies were identified. After removing 14 reviews and other types of articles, 69 studies were left. Of these, 56 were excluded because they did not report on metformin treatment, and 5 were excluded for involving animal models. This resulted in 8 studies being considered for full-text review [16-23]. According to our predefined inclusion criteria, we excluded one study that did not adhere to the Rotterdam ESHRE/ASRM criteria and used rosiglitazone or metformin treatment [16], as well as one relevant abstract [17], and two additional studies [18,19] with incomplete or ambiguous data. Consequently, only four studies were ultimately included in the analysis [20-23]. The supplementary Figure 1 displays the PRISMA flow diagram. The exclusion criteria for the studies

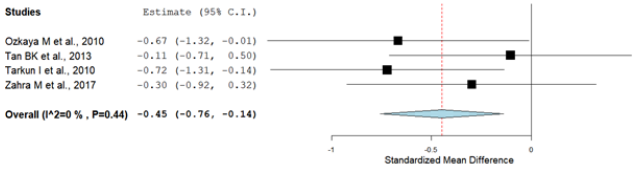

Fig. 1. The results of a meta-analysis on effect of metformin on serum visfatin levels in PCOS.

Table 1. The characteristics of studies included in the meta-analysis.

Variable	Study Name			
Study Characteristics	***Ozkaya M et al., 2010***	***Tan BK et al., 2013***	***Tarkun I et al., 2010***	***Zahra M et al., 2017***
Setting	University Hospital, Turkey	University Hospital, Germany	Turkey	Two tertiary care hospitals, Pakistan
Design	Cross-sectional	Cross-sectional	Cross-sectional	RCT
Subjects	19 PCOS and 21 controls	83 PCOS and 39 controls	24 PCOS and 25 controls	20 PCOS and 20 controls
PCOS Characteristics				
PCOS Criteria	Rotterdam ESHR/ASRM	Rotterdam ESHR/ ASRM	Rotterdam ESHR/ ASRM	Rotterdam ESHR/ ASRM
PCOS n	19	21	24	20
Age (years)	25.1	28	25.2	25.8
BMI (kg/m^2)	27.1	32.8	31.7	26.7
FBG	92.2 mg/dL	5.1 mmol/L	92 mg/dl	100.2 mg/dL
INS	16.5 µIU/mL	70 pmol/L	10.9 µIU/mL	17.2 IU/L
HOMA-IR	3.7	2.2	2.9	4.2
Visfatin Characteristics				
Method	RIA (Phoenix, USA)	EIA (Phoenix, Aviscera)	ELISA (Phoenix, USA)	Double-antibody sandwich ELISA
Units	ng/mL	ng/mL	ng/mL	ng/mL
Metformin Characteristics				
Dose	850 mg, twice daily	850 mg, twice daily	850 mg, twice daily	500 mg, thrice daily
Duration	3 months	3 months	3 months	3 months

BMI: body mass index, ELISA: enzyme-linked immunosorbent assay, ESHRE/ASRM: 2003 Rotterdam ESHRE/ASRM endocrine criteria, FBG: fasting blood glucose, HOMA-IR: homeostatic model assessment-insulin resistance, INS: insulin, RIA: radioimmunoassay.

included in this review were any cases of hyperandrogenism not attributed to PCOS, as well as other reproductive, metabolic, and endocrine disorders. The average age of PCOS patients ranged from 23 to 28 years, and their body mass index (BMI) varied between 26 and 33 kg/m² across the studies. All studies measured serum visfatin levels, reported in ng/mL. Of these, three studies utilized enzyme immunoassays, while one study employed a radioimmunoassay method [20]. In three studies, metformin was administered at a dosage of 850 mg twice daily [20-22], while one study used a 500 mg dose taken three times a day [23]. The duration of metformin treatment varied: two studies reported a treatment period of 3 months [20,23], and two others reported a 6-month duration [21,22]. Although all studies employed a prospective cross-sectional interventional design, only one study randomly assigned PCOS patients to receive metformin treatment [23]. Table 1 and Supplementary Table 1 provide details on the study characteristics and the NOS quality assessment scores. The studies included in the review exhibited overall good quality, with NOS scores ranging from 6 to 8.

3.2. Impact of metformin on serum visfatin concentrations

The meta-analysis incorporated a total of k=4 studies [20-23]. The standardized mean difference (SMD) observed across these studies varied from -0.72 to -0.10 (Figure 1). The random-effects model estimated the average SMD to be -0.44, with a 95% confidence interval ranging from -0.75 to -0.14. This result indicates a statistically significant deviation from zero (z = -2.85, p = 0.0043). The Q-test indicated that heterogeneity among the true outcomes was minimal (Q(3) = 2.72, p = 0.43, tau² = 0.00, I² = 0.00%). Analysis of the studentized residuals showed that no study had a residual exceeding ±2.49, suggesting that no outliers were affecting the model. Additionally, Cook's distances confirmed that no single study exerted undue influence on the results. Moreover, the sensitivity analysis results depicted in Figure 2 confirmed the robustness of the overall findings from this meta-analysis. Both the rank correlation and regression tests showed no evidence of funnel plot asymmetry (p = 1.00 and p = 0.96, respectively), suggesting that publication bias was not a significant factor. The GRADE certainty of evidence was rated as "Moderate," suggesting that further research could significantly impact our confidence in the effect estimate and potentially alter it (Supplementary Table 2).

3.3. Randomized permuted meta-analysis

The results of randomized permuted meta-analysis using 1000, 10,000, and 100,000 iterations shown in Table 2 indicated that the mean over randomized permutations (SMD -0.44, 95% CI -0.75: -0.14) remained to be statistically significant. This further validates the accuracy of actual meta-analysis outcomes obtained from 4 studies

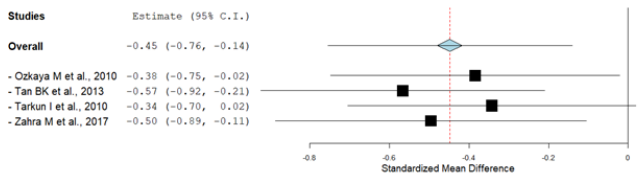

Fig. 2. The results of sensitivity analysis.

Table 2. The results of randomized permuted meta-analysis.

Description	SMD	95%CI
Meta-analysis (4 studies)	-0.45	-0.76: -0.14
Randomized permuted meta-analysis	**Mean over iterations**	**95%CI**
Iterations: 1000	-0.45	-0.76: -0.14
Iterations: 10,000	-0.44	-0.75: -0.14
Iterations: 100,000	-0.45	-0.76: -0.14

SMD: standardized mean difference, CI: confidence interval

(SMD -0.45, 95% CI -0.76: -0.14).

4. Discussion

Although substantial evidence indicates a significant increase in circulating visfatin levels in PCOS patients [11,12], no prior systematic review or meta-analysis has definitively examined the impact of metformin treatment on visfatin levels in this population. This meta-analysis is the first to show a notable decrease in circulating visfatin levels following metformin treatment compared to baseline pretreatment levels. However, the precise mechanisms by which metformin influences visfatin levels remain unclear based on the current evidence.

Visfatin or nicotinamide phosphoribosyl transferase, is predominantly secreted by adipose tissue, though it is also released by skeletal muscle, the liver, and immune cells. This protein has been proposed as a significant biomarker for polycystic ovary syndrome (PCOS), an endocrine disorder characterized by hormonal imbalances, menstrual disorders, ovarian cysts, and metabolic problems like insulin resistance [3,8]. Research indicates that visfatin plays a key role in the development of PCOS. Increased visfatin levels have been reported in women with PCOS, indicating its potential role in the insulin resistance and metabolic issues often associated with this disorder. Visfatin has been shown to have insulin-like effects, enhancing glucose uptake in adipose tissue and skeletal muscle, which might lead to insulin resistance if not properly regulated [9,10]. Additionally, visfatin levels in PCOS are associated with indicators of obesity and metabolic syndrome, suggesting it could be a key factor linking PCOS to metabolic complications.

In addition to its role in metabolism, visfatin plays a part in inflammation and immune responses. It functions as a pro-inflammatory cytokine, enhancing the production of inflammatory substances like tumor necrosis factor-alpha and interleukin-6 (IL-6). Its involvement in both metabolic and inflammatory processes highlights its importance in various metabolic and chronic inflammatory diseases [8-10]. Recent studies suggest that visfatin could be a promising therapeutic target for metabolic and reproductive disorders, including PCOS [20-25]. Research indicates that visfatin levels might be reduced through treatments designed to enhance insulin sensitivity, such as metformin, though the precise mechanisms remain to be studied. The existing evidence regarding the influence of metformin on visfatin levels in PCOS is inconsistent and necessitates further research [20-23].

These inconsistencies may stem from differences in study design, settings, metformin dosages, treatment durations, and the clinical characteristics of the study populations. For instance, while two studies noted a substantial decrease in visfatin levels after metformin treatment [20,22], another two found no significant change from baseline levels [21,23]. Notably, one study that initially reported no significant difference between pre-and post-metformin visfatin levels later observed a significant reduction in visfatin compared to a placebo group in PCOS patients [23]. This meta-analysis reveals a significant reduction in circulating visfatin levels following metformin treatment in PCOS patients compared to their levels before treatment (p=0.004), with no significant heterogeneity observed (I^2=0.00%, p=0.44). Key features of PCOS, including insulin resistance, elevated androgen levels, and anovulatory infertility, are commonly linked with hyperinsulinemia. Metformin is widely utilized as a main therapeutic approach for PCOS, operating through several mechanisms, such as decreasing glucose absorption, lowering androgen levels, stimulating hepatic glucose production, normalizing menstrual cycles, improving abdominal fat distribution, and enhancing peripheral glucose uptake and insulin sensitivity [4]. This meta-analysis seeks to determine if metformin treatment influences visfatin levels, with the hypothesis that it leads to a reduction in visfatin levels in PCOS patients. Our findings indicate that metformin treatment significantly lowers circulating visfatin levels in PCOS patients compared to their baseline levels before treatment. This decrease is likely due to metformin's effectiveness in enhancing insulin sensitivity and addressing metabolic issues associated with PCOS.

Metformin, a widely used treatment for polycystic ovary syndrome (PCOS), is believed to influence visfatin levels through its effects on insulin sensitivity and glucose metabolism. As an insulin-sensitizing agent, metformin enhances peripheral glucose uptake and reduces hepatic glucose production, which may lead to a decrease in insulin resistance—a key feature of PCOS. Given that visfatin is an adipokine with both insulin-mimetic and pro-inflammatory properties, its expression may be modulated by improved insulin sensitivity. It is hypothesized that metformin's ability to lower circulating insulin levels could reduce visfatin expression, as insulin is known to stimulate visfatin production in adipocytes. Additionally, metformin's activation of AMP-activated protein kinase (AMPK) might further influence visfatin levels, as AMPK plays a crucial role in regulating cellular energy homeostasis and inflammation. Therefore, the interaction between metformin, insulin sensitivity, and visfatin expression represents a complex network that could potentially be leveraged to optimize treatment strategies for PCOS, though further investigation into these molecular pathways is necessary to fully understand the underlying mechanisms.

This meta-analysis has both notable strengths and limitations. A key strength is the absence of significant heterogeneity in the meta-analysis results. Although all studies adhered to the Rotterdam criteria for diagnosing

PCOS, variations in sample sizes, metformin dosages, and treatment durations could have impacted the results. Specifically, metformin doses ranged from 300 to 850 mg per day, and treatment durations varied between 3 and 6 months. Among the four studies included, three were cross-sectional and one was a placebo-controlled randomized trial. Despite these variations, the sensitivity analysis confirmed the robustness of the overall findings, and the randomized permuted meta-analysis supported the accuracy of the results. Randomized permuted meta-analysis is a statistical approach that minimizes selection bias by randomizing the inclusion order of studies in a meta-analysis, ensuring a more robust and unbiased aggregation of evidence. This method enhances the reliability of conclusions. Consequently, this meta-analysis highlights a significant effect of metformin on visfatin levels in PCOS. Given the promising results, further well-designed randomized controlled trials with larger sample sizes are needed to clarify the impact of metformin on visfatin levels and its potential as a therapeutic target in PCOS. Due to lack of evidence, further research is needed to determine whether targeting Visfatin directly could enhance therapeutic outcomes. Additionally, examining how metformin's effects on visfatin compare with those of alternative therapies, such as lifestyle modifications or other insulin-sensitizing agents, could offer valuable insights for optimizing PCOS management. This comparison may help determine whether metformin provides unique benefits or if combined approaches could enhance treatment outcomes

In conclusion, this meta-analysis reveals a significant reduction in circulating visfatin levels in PCOS patients following metformin treatment compared to baseline levels. The elevated visfatin levels often seen in PCOS may decrease as metformin addresses associated metabolic issues like insulin resistance. To confirm these findings and explore visfatin's potential as a therapeutic target, further research with well-structured randomized trials is needed.

Conflict of interests
The authors have no conflicts with any step of the article preparation.

Consent for publications
The authors read and approved the final manuscript for publication.

Ethics approval and consent to participate
No human or animals were used in the present research.

Informed consent
The authors declare that no patients were used in this study.

Availability of data and material
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions
The conceptualization of the study was carried out by EPR, HRT, NP, PD, and SRV. Data curation, analysis, methodology, and software development were collaboratively undertaken by EPR, NP, KGM, KLK, AG, PG, and SRV. Supervision and validation responsibilities were managed by SV, NP and SRV. The original draft of the manuscript was written by NP, HRT, and SRV, while the review and editing process involved contributions from SV, AG, PG, and SRV. All authors approved the final manuscript.

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