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RESEARCH ARTICLE OPEN ACCESS

Association of serum GDF15 levels with polycystic ovary syndrome and metformin therapy: A cross-sectional study

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Abstract
Objective: To evaluate serum Growth Differentiation Factor 15 (GDF15) levels in women with polycystic ovary syndrome (PCOS) and to assess the association between metformin therapy and GDF15 concentrations.
Methods: This cross-sectional study included 130 participants: 40 healthy controls, 45 PCOS patients not receiving metformin, and 45 PCOS patients receiving metformin for at least six months. Serum levels of fasting blood glucose, insulin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and GDF15 were measured. Insulin resistance was estimated using the homeostatic model assessment (HOMA-IR). Group comparisons were performed using one-way ANOVA with post-hoc tests.
Results: GDF15 levels were significantly different across groups ($F=39.408$, $p<0.001$). Post-hoc analysis showed that PCOS patients not on metformin had higher GDF15 levels (889±189 pg/mL) than healthy controls (690±125 pg/mL, $p=0.003$). Notably, PCOS patients on metformin showed the highest GDF15 levels (984±152 pg/mL), significantly higher than both untreated PCOS patients ($p<0.05$) and controls ($p<0.001$). HOMA-IR, fasting glucose, insulin, and testosterone were also significantly elevated in PCOS groups compared with controls (all $p<0.001$).
Conclusion: Serum GDF15 levels are elevated in PCOS and are further elevated in association with metformin therapy. GDF15 may serve as a marker of metabolic stress in PCOS and a potential indicator of metformin exposure or response. Longitudinal studies are needed to establish causality.

Keywords: Polycystic ovary syndrome, Growth Differentiation Factor 15, Metformin, Insulin resistance, Biomarkers

Plain English Summary

Polycystic ovary syndrome (PCOS) is a common hormone disorder in women that can cause irregular periods, excess hair growth, and problems with blood sugar control. Metformin is a medicine often used to treat these blood sugar problems. This study measured a protein called GDF15 in the blood of women with PCOS, some taking metformin and some not, and compared them to healthy women. We found that women with PCOS had higher GDF15 levels than healthy women, and those taking metformin had the highest levels. This suggests that GDF15 might be a useful marker to understand how PCOS affects the body and how metformin works. More research is needed to confirm whether metformin directly increases GDF15 or whether women with higher GDF15 are simply more likely to receive metformin.

Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine and metabolic disorder affecting women of reproductive age, with an estimated prevalence of 6–17.8% depending on the diagnostic criteria used (1, 2). The condition is characterised by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, as defined by the revised Rotterdam criteria (3). Beyond reproductive sequelae, PCOS confers

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substantial metabolic risks: approximately 50–70% of affected women exhibit insulin resistance (IR) independent of body mass index, and they have a significantly elevated lifetime risk of type 2 diabetes mellitus, dyslipidaemia, and cardiovascular disease (4, 5).

Growth Differentiation Factor 15 (GDF15), also known as macrophage inhibitory cytokine-1, is a member of the transforming growth factor-β superfamily. It is produced by various cell types in response to cellular stress, inflammation, and metabolic dysfunction (6). Emerging evidence indicates that circulating GDF15 levels are elevated in individuals with impaired fasting glucose and type 2 diabetes, independent of traditional risk factors such as age and body mass index (7). In animal models, high-fat diet-induced obesity increases GDF15 expression, and this elevation correlates with the development of insulin resistance (8).

Metformin, a biguanide drug, is the first-line pharmacological agent for managing metabolic disturbances in PCOS, particularly insulin resistance (9). It improves insulin sensitivity, reduces hepatic gluconeogenesis, and enhances peripheral glucose uptake. Recent studies suggest that metformin may increase circulating GDF15 levels, possibly mediating some of its beneficial effects on energy balance (10). However, clinical data comparing GDF15 levels between metformin-treated and untreated PCOS patients remain limited and inconsistent.

Given this background, the present cross-sectional study aimed to (1) compare serum GDF15 levels between PCOS patients and healthy controls, (2) assess differences in GDF15 levels between PCOS patients receiving metformin therapy and those not receiving metformin, and (3) explore correlations between GDF15 and metabolic/hormonal parameters in PCOS. We hypothesised that GDF15 levels would be elevated in PCOS compared with controls and would be higher in metformin-treated patients, reflecting either a direct drug effect or a marker of more severe metabolic derangement requiring treatment.

Materials and Methods

Study design and ethical approval

This cross-sectional, observational study was conducted at the outpatient gynaecological clinic in Tikrit, Iraq, from November 2025 to February 2026. The study protocol was approved by the Scientific Committee of the College of Medicine, University of Tikrit (Approval Reference: TU/COM/2025/2024). All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments (11). Written informed consent was obtained from all individual participants before enrolment.

Study population

A total of 130 participants were recruited and allocated into three groups:

PCOS with metformin treatment (n=45): Women with a confirmed diagnosis of PCOS who had received metformin therapy (at a stable dose, typically 1500–2000 mg/day) for at least six months before enrolment.

PCOS without treatment (n=45): Women with confirmed PCOS who had never received metformin or any other insulin-sensitising agent.

Healthy controls (n=40): Age-matched women with regular menstrual cycles, no clinical or biochemical signs of hyperandrogenism, and no diagnosis of PCOS.

Inclusion/Exclusion criteria

Inclusion criteria for PCOS groups were women aged 18–45 years with a diagnosis of PCOS based on the revised Rotterdam criteria (presence of at least two of the following: oligo-/anovulation, clinical or biochemical hyperandrogenism, and polycystic ovaries on ultrasound) (3). Exclusion criteria for all participants included pregnancy, malignancy, known thyroid dysfunction, hyperprolactinaemia, congenital adrenal hyperplasia, or any other endocrine disorder that could confound the results.

Clinical and demographic data collection

A standardised questionnaire was used to collect data on age, medical history, medication use, parity, history of infertility, menstrual cycle regularity, and symptoms of hyperandrogenism (hirsutism, acne).

Blood sampling and biochemical analysis

Venous blood samples (approximately 5 mL) were collected from each participant after an overnight fast of 8–12 hours. Fasting blood glucose (FBG) was measured immediately using a clinical biochemistry analyser (RX Daytona, Randox Laboratories, UK). The remaining blood was allowed to clot and centrifuged at 4000 rpm for 10 minutes to separate serum. Serum aliquots were stored at –80°C until analysis.

Serum levels of luteinising hormone (LH), follicle-stimulating hormone (FSH), and total testosterone were quantified using automated chemiluminescence immunoassay methods. Fasting insulin was measured, and insulin resistance was estimated using the homeostatic model assessment for insulin resistance (HOMA-IR): HOMA-IR = (fasting insulin in μU/mL × fasting glucose in mg/dL) / 405.

GDF15 measurement
Serum GDF15 concentrations were determined using a commercially available human GDF15 sandwich enzyme-linked immunosorbent assay (ELISA) kit (catalogue number SL2293Hu, [manufacturer name and city, country to be added]). The assay was performed strictly according to the manufacturer's instructions. All samples were run in duplicate, and the mean values were used for analysis. The detection range and inter- and intra-assay coefficients of variation were as specified by the manufacturer.

Statistical analysis
Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD). Normality of data distribution was assessed using the Shapiro-Wilk test. One-way analysis of variance (ANOVA) was used to compare means among the three groups, followed by Tukey's honest significant difference (HSD) post-hoc test for pairwise comparisons. Pearson's correlation coefficient was used to assess relationships between GDF15 and other continuous variables. A two-sided p-value <0.05 was considered statistically significant.

Results

Participant characteristics and group comparability
The three groups were similar in age (mean age range 28–31 years, p>0.05 for all comparisons). No significant differences were observed in LH or FSH levels across groups (p=0.245 and p=0.323, respectively; Table 1).

GDF15 levels across groups
Serum GDF15 levels differed significantly among the three groups (one-way ANOVA: F=39.408, p<0.001). Post-hoc comparisons revealed that PCOS patients not receiving metformin had significantly higher GDF15 levels than healthy controls (889±189 pg/mL vs. 690±125 pg/mL, p=0.003). Notably, PCOS patients receiving metformin exhibited the highest GDF15 levels (984±152 pg/mL), which were significantly elevated compared with both untreated PCOS patients (p<0.05) and healthy controls (p<0.001). Figure 1 illustrates these group differences.

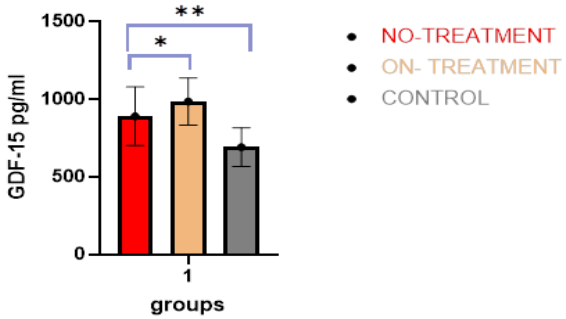


Figure 1: Mean serum GDF15 levels (pg/mL) in healthy controls, PCOS patients without metformin, and PCOS patients with metformin therapy
Error bars represent standard deviation. *p<0.05 vs. untreated PCOS; **p<0.001 vs. control; †p<0.01 vs. control.

Metabolic and hormonal parameters
Table 1 summarises the hormonal and metabolic biomarkers across the three groups. Fasting blood glucose, insulin, HOMA-IR, and testosterone were all significantly elevated in both PCOS groups compared with healthy controls (p<0.001 for each). There was a trend toward lower fasting insulin and HOMA-IR in metformin-treated patients compared with untreated PCOS patients, although this did not reach statistical significance in post-hoc analysis (p=0.08 for HOMA-IR).

Table 1: Comparison of hormonal and metabolic biomarkers between groups

Parameter	No Treatment (n=45)	On Treatment (n=45)	Control (n=40)	F-test	p-value
LH (IU/L)	10.04 ± 3.12	9.95 ± 3.01	9.2 ± 2.9	0.688	0.245 (NS)
FSH (IU/L)	5.82 ± 2.11	5.34 ± 1.72	5.29 ± 1.76	1.141	0.323 (NS)
FBG (mg/dL)	98.80 ± 10.87	102.05 ± 15.89	91.70 ± 8.37	7.715	<0.001
Insulin (µU/mL)	11.48 ± 2.10	9.19 ± 1.59	8.13 ± 1.78	1.64	<0.001
HOMA-IR	2.86 ± 0.44	2.32 ± 0.54	1.81 ± 0.88	0.38	<0.001
Testosterone (ng/mL)	1.07 ± 0.43	1.14 ± 0.33	0.85 ± 0.26	1.232	<0.001
GDF15 (pg/mL)	889 ± 189	984 ± 152	690 ± 125	39.408	<0.001

Data are mean ± standard deviation. NS = not significant; FBG = fasting blood glucose; HOMA-IR = homeostatic model assessment of insulin resistance

Correlations between GDF15 and insulin resistance

In the healthy control group, there was a positive correlation between GDF15 levels and HOMA-IR (r=0.42, p<0.05; Figure 2A). However, in the combined PCOS groups, GDF15 showed a weak negative correlation with HOMA-IR that did not reach statistical significance (r=−0.18, p=0.09). No significant correlation was observed between GDF15 and testosterone levels in PCOS patients (r=0.05, p=0.62; Figure 2B).

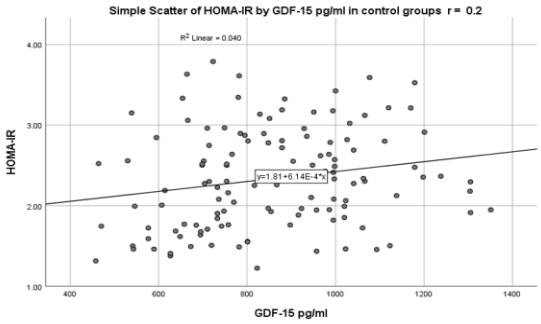


Figure 2A: Scatter plot showing positive correlation between GDF15 and HOMA-IR in healthy controls.

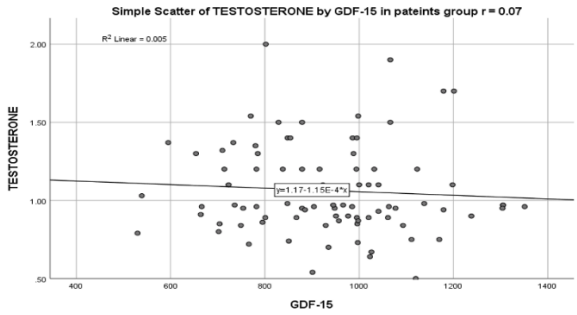


Figure 2B: Scatter plot showing no significant correlation between GDF15 and testosterone in PCOS patients

Discussion

This cross-sectional study provides evidence that serum GDF15 levels are elevated in women with PCOS compared with healthy controls, and that patients receiving metformin therapy have even higher GDF15 concentrations than untreated PCOS patients. These findings align with and extend previous reports showing elevated GDF15 in metabolic disorders, including PCOS (12, 13).

GDF15 elevation in PCOS: a marker of metabolic stress

The observation that untreated PCOS patients had significantly higher GDF15 levels than healthy controls is consistent with the growing literature linking GDF15 to insulin resistance and chronic low-grade inflammation (7, 8). PCOS is characterised by systemic metabolic dysfunction, including hyperinsulinaemia, adipose tissue inflammation, and oxidative stress – all known inducers of GDF15 expression. Thus, elevated GDF15 may reflect the cumulative metabolic burden of PCOS rather than being a direct pathogenic factor. Our finding that GDF15 correlated positively with insulin resistance in healthy controls but not in PCOS patients suggests that once metabolic dysregulation reaches a certain threshold, other regulatory mechanisms may override the simple linear relationship. This dissociation has been observed in other chronic metabolic diseases (14).

Association of metformin therapy with higher GDF15 levels

A key and novel finding of this study is the significantly higher GDF15 levels in metformin-treated PCOS patients compared with untreated patients. Although our cross-sectional design cannot prove causation, this association is biologically plausible. Recent mechanistic studies have demonstrated that metformin increases circulating GDF15 through a kidney-dependent pathway involving the area postrema and that GDF15 mediates some of

metformin's effects on energy balance and body weight (10, 15). In animal models, oral metformin increased GDF15 expression predominantly in the distal intestine and kidney, leading to reduced food intake and improved metabolic parameters (10). Our findings in humans are consistent with this proposed mechanism: metformin use is associated with elevated GDF15, which may contribute to its therapeutic effects.

Alternatively, the higher GDF15 levels in treated patients could reflect channelling bias, that is, women with more severe metabolic derangements were preferentially prescribed metformin. We attempted to minimise this by including only patients on stable metformin therapy for at least six months, but residual confounding by disease severity cannot be excluded. The fact that metformin-treated patients in our study had slightly (though not significantly) lower HOMA-IR than untreated patients suggests that treatment was effective, yet GDF15 remained higher, which supports a direct drug effect rather than simply reflecting underlying metabolic severity.

Clinical implications

If confirmed in longitudinal studies, GDF15 could serve as a useful biomarker for monitoring metformin exposure or response in PCOS. Unlike glucose or HOMA-IR, which can normalise with treatment, GDF15 appears to remain elevated or even increase. This might be advantageous for assessing long-term adherence or for identifying patients who would benefit most from metformin. However, before clinical application, prospective studies should define reference ranges and establish whether GDF15 levels predict long-term metabolic outcomes in PCOS.

Study limitations and future directions

Several limitations must be acknowledged. First, the cross-sectional design precludes any causal inference. We cannot determine whether metformin directly increases GDF15 or whether women with intrinsically higher GDF15 are more likely to receive metformin. A randomised controlled trial with baseline and post-treatment measurements is needed. Second, we did not collect data on body mass index (BMI) or waist circumference, which are important confounders of both GDF15 levels and insulin resistance. Third, metformin dose and adherence were not biochemically verified (e.g., by drug levels or pill counts). Fourth, the study was conducted at a single centre in Iraq, limiting generalisability to other populations. Fifth, the GDF15 ELISA kit details were incompletely recorded; future studies should provide full assay characteristics. Finally, the sample size was relatively modest, and we were unable to perform multivariate adjustment for potential confounders.

Future research should prioritise: (1) longitudinal studies with repeated GDF15 measurements before and after metformin initiation; (2) investigation of GDF15 as a predictor of metformin response (e.g., improvement in menstrual cyclicity or ovulation); (3) exploration of whether GDF15 mediates any of metformin's reproductive benefits; and (4) studies including objective measures of adiposity and dietary intake.

Conclusion

In this cross-sectional study, women with PCOS had significantly higher serum GDF15 levels than healthy controls. Moreover, PCOS patients receiving metformin therapy exhibited the highest GDF15 concentrations, suggesting that metformin use is associated with GDF15 elevation. GDF15 may serve as a marker of metabolic stress in PCOS and a potential indicator of metformin exposure. However, given the observational design, causal relationships cannot be established. Randomised controlled trials are urgently needed to determine whether metformin directly increases GDF15 and whether GDF15 levels predict treatment outcomes in PCOS.

List of Abbreviations

ANOVA: Analysis of variance
BMI: Body mass index
ELISA: Enzyme-linked immunosorbent assay
FBG: Fasting blood glucose
FSH: Follicle-stimulating hormone
GDF15: Growth Differentiation Factor 15
HOMA IR: Homeostatic model assessment of insulin resistance
HSD: Honest significant difference
IR: Insulin resistance
LH: Luteinising hormone
PCOS: Polycystic ovary syndrome
SD: Standard deviation
SPSS: Statistical Package for the Social Sciences
T2DM: Type 2 diabetes mellitus
TGF β: Transforming growth factor beta

Declarations

Ethics approval and consent to participate

The study was approved by the Scientific Committee of the College of Medicine, University of Tikrit (Approval Reference: TU/COM/2025/2024). The study was performed in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study.

Consent for publication
All authors gave consent for the publication of this work under the Creative Commons Attribution Non-Commercial 4.0 license.

Data availability
The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

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Author contributions
IDK worked on the conceptualisation, methodology, investigation, formal analysis, data curation, writing the original draft, writing the review & editing, visualisation and project administration.
ZSA worked on the conceptualisation, methodology, validation, resources, writing the review & editing and supervision.

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