Raheem *et. al.* Babcock Univ. Med. J.2025 8(1):
https://doi.org/10.38029/babcockuniv.med.j..v8i1.

eISSN: 2756-4657

RESEARCH ARTICLE OPEN ACCESS

Elevated Serum Fibroblast Growth Factor 21 and Lipid Profile alterations in Polycystic Ovary Syndrome: A case-control study

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Submitted: 15th January 2024
Accepted: 17th March 2025
Published: 30th June 2025
ID: Orcid ID

Abstract
Objective: Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder that not only disrupts reproductive function but is also associated with significant metabolic and hepatic disturbances. This case-contol study aimed to compare metabolic and liver function parameters between women with PCOS and healthy controls, with a focus on the potential role of fibroblast growth factor 21 (FGF21) as a diagnostic biomarker.
Methods: Participants were selected according to the Rotterdam criteria and included age- and BMI-matched women with PCOS and healthy controls. Fasting blood samples were collected from all subjects to measure serum lipid profiles, liver enzymes, and FGF21 concentrations. Standard enzymatic colourimetric assays were used for lipid measurements, while liver enzymes were determined via spectrophotometric methods. Circulating FGF21 levels were quantified using a commercially available ELISA kit.
Results: PCOS patients exhibited significantly higher serum FGF21 levels (122 ± 42.3 ng/mL) compared to controls (63.5 ± 21.5 ng/mL, $p < 0.001$). ROC curve analysis identified an optimal FGF21 cutoff value of approximately 87.78 ng/mL, yielding a sensitivity of 91% and specificity of 90% for PCOS diagnosis.
Conclusion: The study reinforces the association of PCOS with distinct metabolic and hepatic abnormalities. The elevated levels of FGF21 in PCOS patients may reflect a compensatory response to metabolic stress and point to its promise as a novel diagnostic marker. These findings highlight the importance of comprehensive metabolic screening in PCOS and may inform future therapeutic approaches.

Keywords: Polycystic Ovary Syndrome (PCOS), Fibroblast Growth Factor 21 (FGF21), Metabolic Biomarker, Insulin Resistance, Endocrine Disorders, Diagnostic Marker

Plain English Summary

Polycystic ovary syndrome (PCOS) is a common condition in reproductive-age women whereby the woman has a hormonal imbalance and her ovaries create excess hormones. This condition disrupts women's reproductive function and also affects their metabolic and liver functions. This study aimed to compare the metabolic and liver function variables between women with PCOS and healthy women without PCOS. This research focuses on the potential role of fibroblast growth factor 21 (FGF21) a protein that regulates metabolism and energy homeostasis- as a biological measurement that helps diagnose PCOS. Using the case-control study design, participants were selected according to the Rotterdam criteria and included age- and BMI-matched women with PCOS and health controls. The study findings showed that PCOS patients exhibited significantly higher serum FGF21 levels (122 ± 42.3 ng/mL) compared to controls (63.5 ± 21.5 ng/mL, $p < 0.001$). This study strengthens the association of PCOS with distinct metabolic and hepatic abnormalities.

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Background

Polycystic ovary syndrome (PCOS) affects approximately 8% to 13% of women of reproductive age (1). It is characterized by a variety of clinical manifestations, including menstrual cycle dysfunction, biochemical and phenotypical hyperandrogenism, and anovulation, which can lead to infertility (2). Beyond its reproductive implications, PCOS is also strongly associated with metabolic complications such as insulin resistance, abnormal lipid profiles, and an increased likelihood of developing type 2 diabetes and cardiovascular disease (3). Although the exact causes of PCOS remain elusive, current evidence suggests that a combination of genetic and environmental factors plays a role in its development (1, 4).

A key element in the metabolic complications of PCOS is insulin resistance (5). This condition not only aggravates hyperandrogenism by boosting ovarian androgen synthesis but also contributes to adverse lipid alterations, which often result in elevated cholesterol and triglyceride levels (6). Moreover, insulin resistance is a recognized contributor to non-alcoholic fatty liver disease (NAFLD), a disorder that appears to be increasingly common among women with PCOS (7). Elevated levels of liver enzymes such as AST and ALT are indicative of hepatic steatosis and low-grade inflammation, suggesting that subclinical liver dysfunction may be an underappreciated component of PCOS (8).

In recent years, research has increasingly focused on fibroblast growth factor 21 (FGF21), a liver-derived hormone that plays a critical role in managing glucose and lipid metabolism (9, 10). Under conditions of metabolic stress, such as those induced by insulin resistance, the FGF21 level typically rises (11). Elevated serum FGF21 has been observed in metabolic disorders like obesity and type 2 diabetes, and in the context of PCOS, increased FGF21 may reflect a compensatory mechanism against metabolic disturbances(10). Alternatively, some studies have proposed that high FGF21 concentrations could indicate a state of resistance to its metabolic effects, where the hormone's efficacy is diminished at the tissue level (12, 13).

Based on these insights, our study was designed to evaluate the metabolic and liver profiles of women with PCOS by comparing conventional markers—such as lipid levels and liver enzymes—with circulating FGF21 concentrations, against a backdrop of healthy controls. This dual focus aims not only to further clarify the metabolic anomalies associated with PCOS but also to assess the potential of FGF21 as a diagnostic biomarker, which might facilitate earlier detection and improved management of the syndrome.

While previous research has shed light on these relationships, varying results—possibly due to differences in study populations, diagnostic methods, or research designs- underscore the necessity for further investigation. Consequently, our study aims to contribute a comprehensive evaluation of these factors within a clearly defined cohort, thereby enhancing our overall understanding of PCOS and its metabolic repercussions.

Materials and Methods

Study Design and Participants

This case-control study was conducted at Maysan Child and Birth Hospital between August 2024 and January 2025. Sixty women diagnosed with polycystic ovary syndrome (PCOS) were enrolled based on the Rotterdam criteria, while an equal number of healthy women with regular menstrual cycles and no signs of hyperandrogenism were recruited as controls.

Patients and Control Selection

Women within the designated age range(18- 45 Years), who met the PCOS diagnostic criteria- namely, The Rotterdam Criteria, the presence of at least two out of three features: oligo/anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology- were included (14). Exclusion criteria consisted of pregnancy, recent use of hormonal or lipid-modifying therapies, and known hepatic or renal diseases.

Anthropometric Measurements and Sample Collection

After an overnight fast, venous blood samples were collected from all participants. Anthropometric data, including height and weight, were recorded to calculate body mass index (BMI). The blood samples were centrifuged to separate serum, which was then aliquoted and stored at –80°C for subsequent biochemical analyses.

Biochemical Measurements

Serum total cholesterol and triglyceride levels were measured using established enzymatic colourimetric assays. Liver enzymes, specifically aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were quantified using an automated spectrophotometric method based on the Reitman-Frankel procedure. Circulating fibroblast growth factor 21 (FGF21) concentrations were determined using a commercial enzyme-linked immunosorbent

assay (ELISA) kit, following the manufacturer's instructions.

Statistical Analysis

The data analysis was conducted using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables are reported as mean ± standard deviation (SD), while categorical variables are presented as frequencies and percentages. The normality of continuous data was assessed using the Shapiro-Wilk test. For comparisons between groups, the student's t-test was applied to normally distributed data, whereas the Mann-Whitney U test was used for non-normally distributed data. Categorical variables were analyzed using the Chi-square test. To assess the diagnostic performance of serum FGF21 in detecting PCOS, Receiver Operating Characteristic (ROC) curve analysis was performed, reporting key parameters such as sensitivity, specificity, and the area under the curve (AUC). A p-value of less than 0.05 was considered statistically significant for all analyses (15).

Results

In Table 1, the demographic characteristics of the control and PCOS groups were compared. The control group has a mean age of 27.8 ± 7.8 years (range 18–45), while the PCOS group has a mean age of 23.24 ± 4.5 years (range 16–38). Although the control group appears older on average, this difference was not statistically significant (p = 0.09). The mean BMI for the control group was 26.4 ± 3.6 (range 20–28), whereas the PCOS group had a mean BMI of 27.1 ± 4.8 (range 20–34). This difference was also not statistically significant (p = 0.43).

Table 1. Demographic Characteristics of control and PCOS groups

Characteristic	Control *n* = 60	PCOS *n* = 60	*p*
Age (years)			
Mean ±SD	27 8. ± 7.8	24.3 ± 4.5	0.09 **I NS**
Range	18 – 45	18 – 36	
BMI (kg/m²)			
Mean ±SD	26.4 ± 3.6	27.1 ± 4.8	0.43 **I NS**
Range	20 – 36.7	22 – 46	

n: number of cases; SD: standard deviation; I: independent samples t-test. NS: Not Significant

In Table 2, both cholesterol and triglyceride levels are markedly higher in the PCOS group compared to the control group. The mean cholesterol concentration for the PCOS group was 164 ± 30.1 mg/dL (range 112–225), which was significantly greater than the control group's mean of 120.9 ± 30.8 mg/dL (range 88–169), with a p-value < 0.001. Similarly, triglyceride levels were substantially elevated in the PCOS group, averaging 165 ± 59 mg/dL (range 102–457) compared to 107 ± 19.7 mg/dL (range 75–192) in the control group, also at a p-value < 0.001.

Table 2: Comparison of total cholesterol and triglyceride levels between control and PCOS groups

Characteristic	Control *n* = 60	PCOS *n* = 60	*p*
Cholesterol (mg/dL)			
Mean ±SD	120.9 ± 30.8	164 ± 30.1	<0.001 I***
Range	88– 169	112 – 225	
Triglycerides (mg/dL)			
Mean ±SD	107 ± 19.7	165 ± 59	<0.001 I***
Range	75 – 140	102 – 457	

n: number of cases; SD: standard deviation; I: independent samples t-test; Statistical significance was indicated by ***p<0.001.

In Table 3, the mean AST level in the PCOS group (51.1 ± 17.2 U/L, range 23–112) was significantly higher than in the control group (19.4 ± 5.5 U/L, range 12–33) with a p-value < 0.001. Similarly, the mean ALT level was markedly elevated in the PCOS group (32.6 ± 13.3 U/L, range 16–81) compared to the control group (13.8 ± 4.2 U/L, range 8–25), also at p < 0.001.

Table 3: Comparison of liver aminotransferase levels (AST and ALT) between control and PCOS Groups

Characteristic	Control *n* = 60	PCOS *n* = 60	*p*
AST(U/L)			
Mean ±SD	19.4 ± 5.5	51.1 ± 17.2	<0.001 I***
Range	12 – 33	23 – 112	
ALT(U/L)			
Mean ±SD	13.8 ± 4.2	32.6 ± 13.3	<0.001 I***
Range	8 – 25	16 – 81	

n: number of cases; SD: standard deviation; I: independent samples t-test; Statistical significance was indicated by ***p<0.001

In Table 4, serum FGF21 concentrations are substantially elevated in the PCOS group, with a mean of 122 ± 42.3 ng/mL (range 60.5–223) compared to 63.5 ± 21.5 ng/mL (range 12.3–104.9) in the control group. This difference was statistically significant (p < 0.001).

Table 4: Serum FGF21 concentration levels between control and PCOS group

Fibroblast Growth Factor 21 (ng/mL)			
Mean ±SD	63.5 ± 21.5	122 ± 42.3	<0.001 I***
Range	12.3 – 104.9	60.5 – 223	

n: number of cases; SD: standard deviation; I: independent samples t-test; Statistical significance was indicated by ***p<0.001

In Table 5, the ROC curve analysis demonstrated that a serum FGF21 cut-off of 87.78 ng/mL yielded high diagnostic accuracy for PCOS, with a sensitivity of 91% and specificity of 82%. The positive and negative predictive values (92% and 90%, respectively) further underscore its clinical utility. The area under the ROC curve (AUC) was 0.95 (p < 0.001), indicating excellent overall diagnostic performance.

Table 5: Analysis of the ROC curve for FGF21 in PCOS Diagnosis

Variables	Cut-off value	Sens**%	Spec%	PPV**	NPV	AUC%	P-value (AUC= 0.05)
Fibroblast Growth Factor 21 (ng/mL)	**> 87.78**	**91**	**90**	**92**	**86**	**92**	**0.001****

Sens: Sensitivity; Spec: Specificity; PPV: positive predictive value; NPV: negative predictive value; AUC: area under curve

Figure 1 visually corroborates these findings, showing a clear separation between PCOS and control groups based on FGF21 levels.

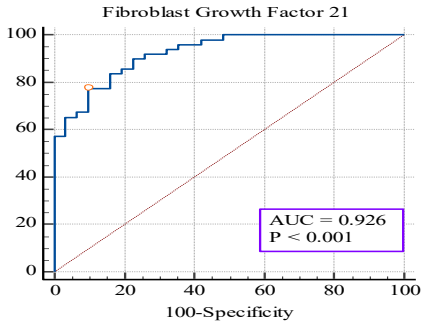

Figure 1: ROC Curve Analysis for Serum Fibroblast Growth Factor 21 in PCOS Diagnosis

Discussion

Women with PCOS exhibited significantly elevated total cholesterol (TC) and triglyceride (TG) levels compared to controls, indicating lipid metabolism disturbances. While LDL, HDL, and fasting glucose were not assessed here, TC and TG are recognized as primary predictors of cardiovascular risk in PCOS. Liver enzymes—

namely AST and ALT—were also significantly increased in the PCOS group, indicating possible hepatic stress. Furthermore, serum FGF21 levels were substantially elevated in PCOS, and our ROC analysis revealed that FGF21 could serve as a highly sensitive and specific biomarker for distinguishing PCOS from controls.

Our lipid findings align with numerous reports that link PCOS to dyslipidaemia and heightened cardiovascular risk (3, 16). Women with PCOS exhibited elevated AST and ALT levels, which may indicate hepatic stress. However, the observed AST/ALT ratio in PCOS vs. in controls does not align with the typical pattern of early NAFLD, where ALT predominates over AST (17). While NAFLD is prevalent in PCOS (18), our findings suggest that AST/ALT elevations in this cohort may reflect alternative mechanisms, such as systemic inflammation driven by insulin resistance or mitochondrial dysfunction in hepatocytes (19). For example, hyperinsulinemia in PCOS is associated with oxidative stress, which can disproportionately elevate AST due to its mitochondrial isoform (mAST) (20). Additionally, subclinical cardiovascular dysfunction, common in PCOS, may contribute to hepatic congestion and elevated AST (7). Further studies incorporating liver imaging (e.g., FibroScan) or histopathology are needed to confirm hepatic steatosis and rule out other aetiologies.

Our observation of elevated FGF21 levels in PCOS is broadly consistent with studies indicating that FGF21 often rises in states of metabolic dysfunction, including obesity, insulin resistance, and type 2 diabetes (10, 21). However, a few researchers have documented normal or even lower FGF21 levels in certain subgroups of PCOS patients (22). These inconsistencies may be attributable to different inclusion criteria, ethnic variations, or variability in PCOS severity and comorbidities.

The pronounced dyslipidaemia observed in PCOS could be explained by insulin resistance, a core feature of the syndrome that disrupts normal lipid metabolism (23). Insulin resistance stimulates lipolysis and alters lipase activity, leading to higher triglyceride levels and lower high-density lipoprotein (HDL) cholesterol (23). Chronic hyperinsulinemia may promote increased hepatic very-low-density lipoprotein (VLDL) production, thereby elevating circulating triglycerides and total cholesterol (24). Additionally, androgen excess in PCOS may exacerbate abnormal lipid profiles by altering hepatic lipid handling (25). Elevated liver enzymes in PCOS are often attributed to hepatic steatosis and inflammation arising from insulin resistance and hyperandrogenemia (26). Insulin resistance can drive ectopic fat deposition in the liver, leading to steatosis and subsequent hepatocellular injury, which is reflected by increased AST and ALT (27). It is plausible that, in our study population, these metabolic perturbations were severe enough to manifest as significantly higher liver enzyme activity.

FGF21 is a hepatokine secreted predominantly by the liver in response to metabolic stress, including excess nutrient intake and insulin resistance (28). In PCOS, heightened insulin resistance and potential hepatic fat accumulation can indeed stimulate FGF21 secretion and FGF21 is often elevated in the context of metabolic syndrome and fatty liver, which may be a feedback mechanism to counteract excessive hepatic free fatty acid exposure and this elevation of FGF21 aims to mitigate the adverse effects of insulin resistance and hepatic fat accumulation, suggesting a complex interplay between these metabolic conditions and FGF21 production (29, 30). Although FGF21 typically improves insulin sensitivity in animal models, elevated circulating levels in humans and PCOS may indicate a state of “FGF21 resistance” at the target tissue level (12, 31). We suggest that chronic exposure to high insulin and free fatty acids might desensitize tissues to FGF21, driving compensatory upregulation of FGF21 production by the liver.

These findings underscore the importance of routine metabolic screening for women with PCOS. Elevated cholesterol, triglycerides, and liver enzymes highlight the increased risk of cardiovascular and hepatic complications, while high FGF21 levels point to potential utility in clinical practice. Our ROC analysis suggests that measuring FGF21 may be a valuable tool in the diagnostic workup of PCOS, particularly for patients presenting with ambiguous symptoms. Early identification of metabolic disturbances could lead to timely interventions such as lifestyle modifications, pharmacotherapy, or closer monitoring to mitigate long-term risks.

A key strength of our study is the comprehensive evaluation of both traditional metabolic markers (lipid profile, liver enzymes) and a novel biomarker (FGF21) in the same study of PCOS and control participants. This approach offers a multifaceted perspective on the pathophysiological underpinnings of PCOS. Additionally, our use of ROC curve analysis provides clinically relevant information on FGF21’s diagnostic performance .However, our sample size, while adequate for detecting significant differences in several parameters, may limit the generalizability of our findings to broader populations. We also relied on a single measurement design, preventing us from drawing firm conclusions about causality or the longitudinal progression of these metabolic disturbances. Furthermore, differences in dietary

habits, genetic backgrounds, or PCOS phenotypes were not fully explored, which may partially account for variability within the PCOS group.

Conclusion

Women with PCOS in our study exhibited significant metabolic disruptions, including dyslipidaemia, elevated liver enzymes, and markedly higher FGF21 concentrations. These results are largely in agreement with previous research on the metabolic challenges associated with PCOS. The mechanistic links likely involved insulin resistance, hyperandrogenemia, and compensatory changes in hepatokine secretion. Clinically, our findings highlight the potential for FGF21 to serve as an adjunctive biomarker for PCOS diagnosis and underscore the need for vigilant metabolic monitoring in affected individuals.

List of Abbreviations

PCOS: Polycystic Ovary Syndrome
FGF21: Fibroblast Growth Factor 21
BMI: Body Mass Index
AST: Aspartate Aminotransferase
ALT: Alanine Aminotransferase
NAFLD: Nonalcoholic Fatty Liver Disease
ELISA: Enzyme-Linked Immunosorbent Assay
ROC: Receiver Operating Characteristic
AUC: Area Under the Curve
SD: Standard Deviation
SPSS: Statistical Package for the Social Sciences
VLDL: Very-Low-Density Lipoprotein
HDL: High-Density Lipoprotein
PPV: Positive Predictive Value
NPV: Negative Predictive Value

Declarations

Ethical approval and consent to participate

Ethics

The study protocol was approved by the Institutional Review Board of Maysan Child and Birth Hospital (Ethical No; 4480) and complied with the principles of the Declaration of Helsinki (32). All participants provided written informed consent before enrollment.

Consent for publication

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

Availability of data and materials

The data and materials associated with this research will be made available by the corresponding author upon reasonable request.

Competing interests

We declare that there are no conflicts of interest associated with this manuscript.

Funding

We declare that this research did not receive any specific grant or funding from public, commercial, or non-profit organizations.

Author contributions

RTH: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing. MMJ: Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

Acknowledgement

Not applicable.

Acknowledgements

We sincerely thank the medical and administrative teams at Maysan Child and Birth Hospital for their invaluable support throughout the study. We also appreciate the Institutional Review Board for granting ethical approval and extend our gratitude to all participants for their time and effort.

Declaration

Conflict of Interest: We declare that there are no conflicts of interest associated with this manuscript.

Financial Disclosures: We declare that this research did not receive any specific grant or funding from public, commercial, or non-profit organizations.

Authors' contributions

T.R.H (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing)

M.M.J (Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing)

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