Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Research on Fibroblast Growth Factor 21 and Its Relationship to Patients with Polycystic Ovary Syndrome and Obesity

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Purpose: Polycystic ovary syndrome (PCOS) is a complex endocrine disorder, and the role of fibroblast growth factor 21 (FGF21), a metabolic regulator, in its pathophysiology remains unclear. In this context, this study aims to evaluate the FGF21 levels in women with PCOS compared to healthy control subjects and investigate the relationship between FGF21 and obesity.

Patients and Methods: The population of this prospective, non-randomized, controlled study comprised consecutive female patients aged 18–55 years who presented to the outpatient clinics of a tertiary hospital between October 2017 and February 2018. At least two of the three parameters of the Rotterdam Consensus Criteria were regarded in diagnosing PCOS. Ninety-two patients with (n=62) and without PCOS (n=30) were categorized based on their BMI values. Participants' serum FGF21 levels were measured, and the relationships between FGF21 levels and parameters such as age, body mass index (BMI), waist circumference, body fat percentage, and homeostasis model assessment insulin resistance (HOMA-IR) were analyzed. The study's primary and secondary outcomes were the difference in serum FGF21 levels between the patient and control groups and the impact of obesity on FGF21 levels in both groups.

Results: The median age of the patient group was significantly lower than the control group (31.5 years vs 24.0 years, $p<0.001$). There was also a significant difference between the groups in HOMA-IR ($p=0.020$). On the other hand, there was no significant difference between the groups in FGF21 level ($p>0.05$). Analysis revealed no significant effects of age or HOMA-IR on FGF21 levels. BMI had a marginal impact on FGF21 levels regardless of PCOS status. Statistically significant positive correlations between FGF21 and DHEAS were detected in the study population (rho=0.282, $p=0.007$) and all PCOS patients (rho=0.364, $p=0.004$).

Conclusion: FGF21 does not appear to play a significant role in the pathophysiology of PCOS or its associated metabolic abnormalities.

Plain Language Summary: PCOS affects many women worldwide, causing irregular periods and metabolic problems. Scientists have been studying various proteins that might explain how PCOS develops. One such protein, FGF21, helps control blood sugar and fat metabolism. This study compared FGF21 levels between women with and without PCOS. We found that FGF21 levels were similar in both groups and unrelated to weight or blood sugar control, suggesting that FGF21 might not be as important in PCOS as previously thought.

Keywords: obesity, insulin resistance, metabolic syndrome, hyperandrogenism, body mass index, hormones

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age.[1,2] Hormonal imbalances, including elevated luteinizing hormone (LH) secretion, altered gonadotropin-releasing hormone (GnRH) pulsatility, hyperinsulinemia, and increased leptin levels, are frequently implicated in the pathophysiology of PCOS.[1,2]

Its diagnosis is based on clinical and/or biochemical androgen excess associated with ovulatory oligo-amenorrhea and polycystic ovarian morphology.[1,3,4] It is closely linked to ectopic fat accumulation and metabolically associated fatty

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liver disease, which are often associated with insulin resistance and reduced energy expenditure. Consequently, women with PCOS are at increased risk of dyslipidemia and central obesity.[1,4]

Organokines are circulating signaling molecules from the liver (hepatokines), adipose tissue (adipokines), and osteocytes.[1,4] Dysregulation of these molecules often leads to alterations in hepatic function and metabolic imbalances, particularly in PCOS patients.[1,4–6]

Fibroblast growth factor 21 (FGF21), a hepatokine predominantly expressed in the liver, pancreas, and white adipose tissue, is critical in regulating glucose and lipid metabolism, insulin sensitivity, energy balance, and adipose tissue function.[7,8] Studies have highlighted its potential as an insulin-sensitizing and lipolysis-suppressing molecule, protecting against systemic metabolic dysregulation, particularly in patients with fatty liver.[1,2,4] Elevated FGF21 levels have been associated with obesity, type II diabetes mellitus, and hepatic steatosis.[4,7] Notably, FGF21 levels correlate proportionally with body mass index (BMI) and are closely linked to visceral obesity.[7,9]

While the findings above suggest that FGF21 may serve as a reliable biomarker for PCOS, particularly in patients with obesity, several studies have reported conflicting results regarding FGF21 levels in women with PCOS.[2,3,10,11] These discrepancies may be attributed to differences in study populations, BMI distribution, or underlying metabolic phenotypes. In addition to the potential interplay between FGF21 levels, nutritional status, and metabolic disturbances in women with PCOS, the association between FGF21 and hormonal imbalances remains a subject of speculation.[7,10,11] Given that LH and androgens are central to the hormonal diagnostic criteria of PCOS, such possible associations suggest that FGF21 plays a role in the hormonal pathophysiology of the disorder, warranting further investigation.[1,2,11]

In this context, this study aims to clarify this discrepancy by evaluating FGF21 levels in women with PCOS compared to healthy control subjects and investigating the relationship between FGF21 and obesity.

Materials and Methods

Study Design

This study was designed as a prospective, non-randomized, controlled study. The local ethics committee approved the study protocol (Approval Date: 03.10.2017, Approval Number: 2017–14/47). The study was conducted with the ethical considerations outlined in the Declaration of the Helsinki.

Population and Sample

The study population comprised consecutive female patients aged 18–55 years who presented to the outpatient clinics of the Department of Endocrinology and Metabolism, Yüksek Ihtisas Hospital, Bursa, Turkey, and were diagnosed with PCOS by satisfying at least two of the three parameters of the Rotterdam Consensus Criteria[12] between October 2017 and February 2018. Pregnant or lactating patients, patients with acute or chronic infection, malignancy, comorbidities, particularly diabetes mellitus, endocrine disorders, and renal failure, patients whose alanine aminotransferase and aspartate aminotransferase levels were 2.5 times higher than normal levels and who have received oral contraceptives, insulin-sensitizing drugs, and statins in the last three months were excluded from the study. The control group consisted of age-matched women who presented to the same outpatient clinics during the study period but did not meet the Rotterdam criteria for PCOS. These women had regular menstrual cycles (21–35 days) and no clinical or biochemical evidence of hyperandrogenism (acne, hirsutism, or alopecia).

Variables and Data Collection

Participants' demographic characteristics were prospectively recorded. Anthropometric characteristics, including weight (kg), height (m), and waist circumference (cm), were measured and then recorded. Body mass index (BMI) values were calculated by dividing their weight (kg) by the square of their height (m2) and recorded. Waist circumferences (cm), ie, the diameter at the midpoint between the lower margin of the last palpable rib and the anterior superior iliac spine,[13] were measured and recorded. Body fat percentages were measured using a Tanita Body Composition Analyzer (Model TBF-300, Tanita Corporation, Itabashi-ku, Tokyo, Japan) after ≥ 8 hours of fasting with sufficient fluid intake[14] and recorded.

Laboratory Measurements

Blood samples were collected from the participants after an overnight fast in the early follicular phase on the third day of the menstrual cycle. These samples were tested for hemoglobin, fasting blood glucose and insulin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), LH, follicle-stimulating hormone (FSH), estradiol (E2), total testosterone, DHEA-S, androstenedione, and 17-hydroxyprogesterone levels. Low-density lipoprotein cholesterol (LDL-C) values were calculated using the following formula:[15] TC-HDL-C- TG/5. Additionally, homeostasis model assessment insulin resistance (HOMA-IR) values were calculated using the following formula: fasting insulin (μIU/mL) x fasting blood glucose/405 2.

An enzyme-linked immunosorbent assay (ELISA) kit (Code: EKO994) (Human FGF21 PicoKine™ ELISA Kit, Sunred Biotechnology Company, Shanghai, China) was used to measure serum FGF21 levels. The standard provided with the kit, initially at a concentration of 960 ng/L, was diluted using the standard dilution buffer and then serially diluted to obtain concentrations of 480 ng/L, 240 ng/L, 120 ng/L, 60 ng/L, and zero ng/L. Before the analysis, serum samples stored at −80°C were thawed at room temperature. The prepared standards and samples were added to antibody-coated wells, followed by enzyme-conjugated antibodies to each well. The plates were sealed with a transparent cover and incubated at 37°C for 1 hour. Following incubation, the contents of the wells were aspirated, and each well was washed five times with 0.35 mL of washing solution. After washing, Chromogen solutions A and B were added to each well. The plates were covered again and incubated at 37°C for 10 minutes. To terminate the enzymatic reaction, 100 μL of stop solution containing 0.5 M H_2SO_4 was added to each well. The optical density of each well was measured at 450 nm using an ELISA plate reader. According to the kit specifications, the assay range was 6–1800 ng/L with a 5.5 ng/L sensitivity.

Study Groups

The patient and control groups were further categorized based on BMI values:[3]

1. PCOS groups (Group PCOS, n=62)
   a. Non-obese PCOS group (BMI <30 kg/m^2) (n=36)
   b. Obese PCOS group (BMI ≥30 kg/m^2) (n=26)
2. Control Groups (Group Control, n=30)
   a. Non-obese control group (BMI <30 kg/m^2) (n=19)
   b. Obese control group (BMI ≥30 kg/m^2) (n=11)

Statistical Analysis

The study's primary outcome was the difference in serum FGF21 levels between the groups, and the secondary outcome was the impact of obesity on FGF21 levels.

The predicted mean matching (PMM) method, which is used for variables with a missing data rate below 20%, was used for FGF21 (ng/mL) with a missing data rate of 11.96% due to the continuous nature of the data and the necessity to preserve sensitivity to outliers. PMM preserves data distribution by estimating missing values through closest matches to observed values, does not require a normality assumption, and is resistant to outliers. Five FGF21 (ng/mL) datasets were generated using PMM. A single complete dataset containing the averages of these five data sets was used for analyses. R-project version 4.4.2 (R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2023, retrieved from https://www.R-project.org), and multiple imputation by chained equations (MICE)[16] software packages were used for imputation of missing data.

The normal distribution characteristics of numerical variables were analyzed using the Shapiro–Wilk test and quantile-quantile (Q-Q) plots. Normally distributed continuous variables were expressed using mean ± standard deviation values, nonnormally distributed continuous variables were expressed as median with minimum and maximum values, and categorical variables were expressed as numbers (n) and percentage (%) values.

In comparing the differences in numerical variables between the two independent groups, independent samples *t*-test was used for numerical variables determined to conform to the normal distribution, including height, HDL-C, LDL-C,

TC, fasting glucose, and FGF21 levels and Mann–Whitney *U*-test was used for numerical variables determined to not conform to the normal distribution, including age, weight, BMI, very low-density lipoprotein cholesterol (VLDL-C), TG, insulin, HOMA-IR, FSH, LH, E2, testosterone, DHEAS, and 17-OH progesterone levels. Specifically, serum FGF21 levels were compared between the Non-obese Control, Non-obese PCOS, Obese Control, and Obese PCOS groups using the Kruskal–Wallis test.

The Pearson's chi-square test was used to compare BMI groups (≥30 kg/m² and <30 kg/m²). Two-way Analysis of variance (ANOVA) was employed to test the hypothesis that FGF21 levels may be affected by PCOS and obesity by assessing the primary effects of PCOS and BMI on FGF21 levels and possible interactions between them. The Levene's test (p=0.145), used for assumption checks, confirmed the homogeneity of variances between the groups. In addition, the approximate linear alignment of points along the 45-degree line in the Q-Q plot demonstrated that the normality assumption was met.

Due to significant differences between the groups in age (p<0.001) and HOMA-IR (p=0.020), Analysis of covariance (ANCOVA) was performed to control the potential confounding effects of these variables on FGF21 levels. The linearity and homogeneity of regression slope assumptions in the ANCOVA model were assessed graphically and found satisfactory.

Pearson's correlation coefficients were used to evaluate the relationship between FGF21 levels and normally distributed variables, including waist circumference and body fat percentage. Spearman's rho correlation coefficients were used for non-normally distributed variables, including age, BMI, and HOMA-IR.

All statistical analyses were performed using the Jamovi project 2.3.28 (Jamovi, version 2.3.28.0, 2023, retrieved from https://www.jamovi.org) and JASP 0.19.2 (Jeffreys' Amazing Statistics Program, version 0.19.2, 2024, retrieved from https://jasp-stats.org) software packages. Probability (p) statistics of ≤ 0.05 were deemed to indicate statistical significance.

Results

The distribution of participants' demographic and anthropometric characteristics by the patient and control groups is shown in Table 1. Accordingly, there was a significant difference between the groups regarding age (p<0.001). The median age of the patient group was significantly lower than the control group (31.5 years vs 24.0 years). There was no significant difference between the groups in other demographic and anthropometric characteristics (p>0.05), including the rate of patients with obesity (BMI>30 kg/m²) (p=0.798).

Table 1 Demographic and Anthropometric Characteristics of Patients with PCOS and the Control Group

Variables	Groups		p-value
	Group PCOS (n=62)	Control Group (n=30)	
Age *(years)*[§]	24.0 [18.0–41.0]	31.5 [21.0–46.0]	**<0.001**[Ω,***]
Height *(cm)*	161.4 ± 7.8	162.1 ± 6.3	0.654[¶]
Weight *(kg)*[§]	72.1 [41.4–116.0]	72.2 [52.7–119.7]	0.957[Ω]
BMI *(kg/m²)*[§]	28.1 [15.6–47.8]	26.0 [19.2–42.9]	0.780[Ω]
Obesity (BMI ≥30*kg/m²)*[‡]	26 (41.9)	11 (36.7)	0.798[β]
Waist circumference *(cm)*[†]	91.5 ± 18.3	87.3 ± 14.6	0.234[¶]
Body fat percentage *(%)*[†]	32.8 ± 10.3	34.0 ± 7.4	0.545[¶]

Notes: [¶]Independent Samples *T*-Test. [Ω]Mann–Whitney *U*-test. [β]Pearson Chi-Square test. [‡]n (%), [†]mean ± standard deviation, [§]median [minimum-maximum]. Bold p-values indicate statistical significance (p≤0.05) as ***p < 0.001.

Abbreviations: PCOS, Polycystic ovary syndrome; BMI, Body mass index.

The distribution of participants' laboratory characteristics by the patient and control groups is shown in Table 2. Accordingly, there were significant differences between the groups in metabolic markers ($p<0.05$). Insulin (11.7 vs 9.1 U/L, $p=0.006$) and HOMA-IR (2.5 vs 2.0, $p=0.020$) values were significantly higher in the patient group than in the control group, while TC (173.5 vs 190.8 mg/dL, $p=0.031$) and LDL-C (99.2 vs 120.1 mg/dL, $p=0.003$) levels were significantly lower. Hyperandrogenism markers, including testosterone (54.3 vs 38.1 ng/dL, $p=0.001$), DHEAS (245.5 vs 154.0 ug/dL, $p=0.001$), and 17-OH progesterone (0.6 vs 0.3 ng/mL, $p=0.001$) levels were significantly higher in the patient group than in the control group. On the other hand, there was no significant difference between the patient and control groups in FGF21 level (150.1±48.2 vs 154.7±47.4 ng/mL, respectively, $p=0.669$).

When age was added to ANCOVA as a covariate, it was determined that there was no significant difference between the patient and control groups in FGF21 level ($p=0.298$) and that age had a marginal but nonsignificant effect on FGF21 levels ($p=0.100$). Similarly, when HOMA-IR was added to ANCOVA as a covariate, it was determined that there was no significant difference between the patient and control groups in FGF21 level ($p=0.298$) and that HOMA-IR did not have any effect on FGF21 levels ($p=0.649$). These results suggest that FGF21 levels were similar between the groups, independent of age and insulin resistance (Figure 1).

Table 2 Laboratory Characteristics and Biochemical Parameters of Patients with PCOS and the Control Group

Variables	Groups		p-value
	Group PCOS (n=62)	Control Group (n=30)	
Fasting glucose *(mg/dL)*†	91.1 ± 9.8	88.4 ± 7.2	0.145¶
Total cholesterol *(mg/dL)*†	173.5 ± 31.9	190.8 ± 36.8	**0.031**¶,*
HDL cholesterol *(mg/dL)*†	53.3 ± 10.4	52.8 ± 10.0	0.835¶
LDL cholesterol *(mg/dL)*†	99.2 ± 28.1	120.1 ± 31.3	**0.003**¶,**
VLDL cholesterol *(mg/dL)*§	15.4 [5.8–64.6]	15.5 [1.4–43.8]	0.585Ω
Triglyceride *(mg/dL)*§	77.0 [29.0–323.0]	78.0 [34.0–218.7]	0.79Ω
Insulin *(U/L)*§	11.7 [2.9–47.0]	9.1 [3.3–21.1]	**0.006**Ω,**
HOMA-IR§	2.5 [0.5–9.7]	2.0 [0.6–4.8]	**0.020**Ω,*
FSH *(mIU/mL)*§	6.5 [2.6–12.2]	6.4 [2.5–24.7]	0.489Ω
LH *(mIU/mL)*§	6.4 [1.3–48.2]	5.2 [2.2–12.2]	0.119Ω
Estradiol *(pg/mL)*§	52.4 [20.3–334.0]	48.4 [20.4–159.0]	0.980Ω
Testosterone *(ng/dL)*§	54.3 [20.9–132.0]	38.1 [21.0–73.5]	**0.001**Ω,**
DHEAS *(ug/dL)*§	245.5 [42.5–564.0]	154.0 [34.0–402.0]	**0.001**Ω,**
17-OH progesterone *(ng/mL)*§	0.6 [0.1–2.2]	0.3 [0.1–1.2]	**0.001**Ω,**
FGF21 *(ng/mL)*†	150.1 ± 48.2	154.7 ± 47.4	0.669#

Notes: ¶Independent Samples *T*-Test. ΩMann–Whitney *U*-test. #Covariance analysis was performed with age and HOMA-IR as covariates. †mean ± standard deviation, §median [minimum-maximum]. Bold p-values indicate statistical significance ($p\leq0.05$) as *: $p<0.05$, **$p<0.01$.

Abbreviations: PCOS, Polycystic Ovary Syndrome; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; VLDL, Very Low-Density Lipoprotein; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; FSH, Follicle Stimulating Hormone; LH, Luteinizing Hormone; DHEAS, Dehydroepiandrosterone Sulfate; FGF21, Fibroblast Growth Factor 21.

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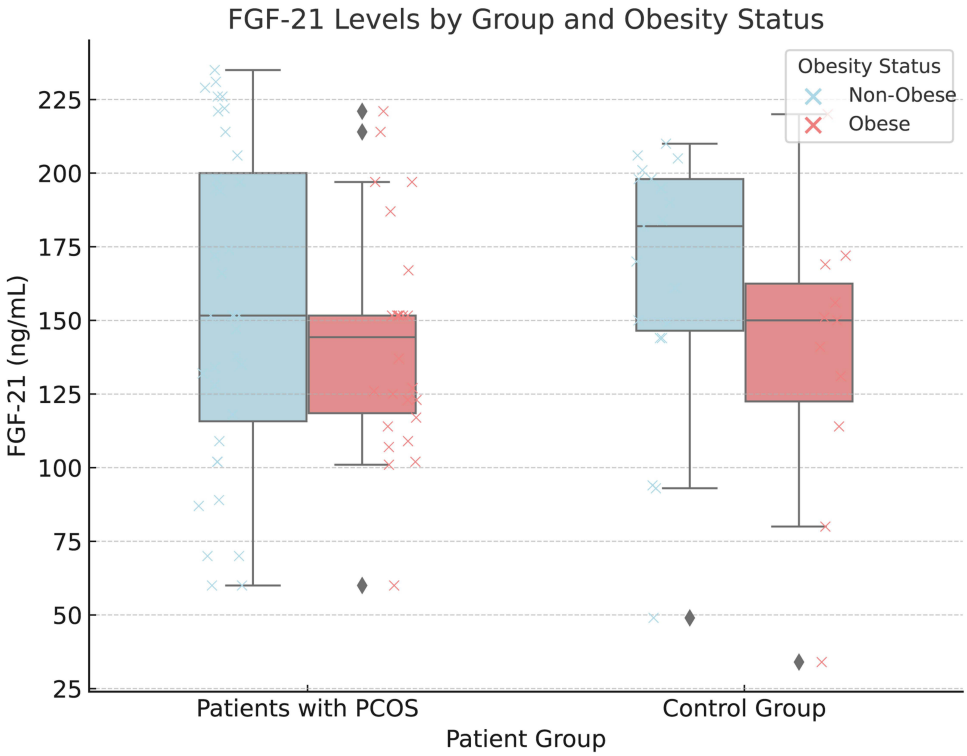

Figure 1 Box plot illustrating the distribution of FGF21 levels (ng/mL) among groups categorized by patient groups (PCOS and control) and obesity status (Non-Obese and Obese), with individual data points overlaid for detailed visualization.

Two-way ANOVA revealed no significant difference in FGF21 levels between the groups independent of BMI (p=0.852). On the other hand, it was found that BMI had a marginal, yet not significant, effect on FGF21 levels independent of PCOS status (p=0.078). There was no significant relationship between the PCOS status and BMI (p=0.526) (Table 3).

FGF21 levels showed no significant differences across the four study groups, based on obesity and PCOS (p=0.284) (Table 4).

Table 3 Distribution of FGF21 Levels According to BMI Groups in Patients with PCOS and the Control Group

Groups	BMI Group	N	Mean ± SD	SE [95% CI]	CV
Control Group	BMI<30 kg/m²	19	164.37 ± 44.74	10.26 [143.85–184.89]	0.272
	BMI≥30 kg/m²	11	138.00 ± 49.29	14.86 [108.28–167.72]	0.357
Group PCOS	BMI<30 kg/m²	36	155.38 ± 54.31	9.05 [137.28–173.48]	0.350
	BMI≥30 kg/m²	26	142.90 ± 37.95	7.44 [128.02–157.78]	0.266

Notes: Assumption Tests: Homogeneity of variances (Levene): p=0.145, Normality: Q-Q plot points forming approximately a straight line along the 45-degree line. Two Way ANOVA Results: Group effect: p=0.852, BMI group effect: p=0.078, Group × BMI interaction: p=0.526.
Abbreviations: BMI, Body mass index; N, Sample size; SD, Standard deviation; SE, standard error; CI, confidence interval; CV, coefficient of variation.

Table 4 Comparison of FGF21 Levels-Based Obesity and PCOS

Variables	Non-obese Control (n=19)	Non-obese PCOS (n=36)	Obese Control (n=11)	Obese PCOS (n=26)	p-value
FGF21 *(ng/mL)*	182.0 [49.0–210.0]	151.6 [60.0–235.0]	150.0 [34.0–220.0]	144.3 [60.0–221.0]	0.284

Notes: Data are presented as median [minimum—maximum] values. Due to the non-normal distributions of variables, non-parametric tests (Kruskal–Wallis) were used for group comparisons.
Abbreviations: PCOS, Polycystic ovary syndrome; FGF21, Fibroblast Growth Factor 21.

Table 5 Correlation Analysis Results Between FGF21 and Other Variables

Variables		r	p-value
Variable 1	**Variable 2**		
FGF21	- Age	−0.178	0.166[tt]
	- Body mass index	−0.178	0.165[tt]
	- Waist circumference	−0.128	0.323[t]
	- Body fat percentage	−0.102	0.429[t]
	- HOMA-IR	−0.173	0.179[tt]

Notes: [t]Pearson correlation coefficient was used. [tt]Spearman's rho correlation coefficient was used.
Abbreviations: FGF21, Fibroblast Growth Factor 21; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance.

Table 6 Spearman Correlation Coefficients Between FGF21 and Hormonal Parameters

	Variables	All Subjects (PCOS + Control)		All PCOS Patients (Obese + Non-obese)		All Obese Patients (PCOS+ and PCOS-)	
		r	p-value	r	p-value	r	p-value
FGF21	**FSH**	−0.027	0.798	−0.138	0.285	0.062	0.717
	LH	−0.125	0.235	−0.147	0.253	0.088	0.603
	Estradiol	−0.130	0.216	−0.104	0.423	0.050	0.771
	Testosterone	−0.069	0.511	0.059	0.649	−0.239	0.155
	DHEAS	**0.282**	**0.007****	**0.364**	**0.004****	0.152	0.369
	17-OH Progesterone	−0.085	0.422	−0.055	0.669	−0.108	0.523

Notes: Bold values indicate statistically significant correlations (p≤0.05) as **p <0.01.
Abbreviations: FGF21, Fibroblast Growth Factor 21; FSH, Follicle-Stimulating Hormone; LH, Luteinizing Hormone; DHEAS, Dehydroepiandrosterone Sulfate; PCOS, Polycystic Ovary Syndrome.

The results of the correlation analyses are shown in Table 5. Accordingly, FGF21 level had a weak negative correlation with age (r=−0.178, p=0.166), BMI (r=−0.178, p=0.165), waist circumference (r=−0.128, p=0.323), body fat percentage (r=−0.102, p=0.429), and HOMA-IR (r=−0.173, p=0.179) (p>0.05).

Table 6 presents the results of the correlation analyses between FGF21 levels and sex hormones in different patient subgroups. Analysis of the entire study population revealed a statistically significant positive correlation between FGF21 and DHEAS (rho=0.282, p=0.007). This relationship remained robust and even strengthened when exclusively analyzing the PCOS patient cohort (rho=0.364, p=0.004). However, this correlation was not maintained in the obesity-only subgroup (rho=0.152, p=0.369).

No statistically significant correlations were identified between FGF21 and other hormonal parameters, including FSH, LH, estradiol, testosterone, and 17-OH progesterone (p>0.05).

Discussion

The study findings showed that FGF21 was not a significant factor in developing PCOS and that age, BMI, waist circumference, body fat percentage, and HOMA-IR were not correlated with FGF21 levels.

An experimental study demonstrated that adolescent prenatally androgenized sheep exhibited decreased FGF21 signaling in subcutaneous adipose tissues and reduced hepatic expression and circulating concentrations of FGF21.[8] However, the study found that circulating FGF21 levels, which were significantly low during adolescence and early adulthood, returned to normal in adulthood by 30 months.

Although the study's authors suggested that prenatal androgen overexposure is a realistic clinical model for PCOS, we hypothesized that complex interactions exist between hyperandrogenism and its metabolic consequences on FGF21 levels. There are conflicting findings regarding FGF21 levels in patients with PCOS.[1–4,7,10,17,18] Garcia-Beltran et al[1]

demonstrated significantly higher levels of FGF21 in adolescents with PCOS than in control girls. Several other studies have reported similar findings.[3,11,18] On the other hand, in their study, they found that nonalcoholic fatty liver disease was significantly associated with FGF21 levels in PCOS patients. They stated that a one pg/mL increase in FGF21 concentration increased the likelihood of fatty liver disease by 1%. Therefore, FGF21 may be a potential biomarker for hepatic disease in adolescents with PCOS. Giannouli et al found no significant difference in FGF21 concentrations between PCOS patients and healthy control subjects,[4] which aligns with our findings and several other studies.[2,10,17]

These inconsistencies highlighted the heterogeneity of PCOS and the complex metabolic and hepatic factors influencing FGF21 levels. The lack of significant differences in FGF21 levels between PCOS patients and healthy control subjects may be attributable to variations in the characteristics of the studies' populations, such as the degree of hyperandrogenism, hepatic steatosis, and insulin resistance, as well as methodological differences, including the timing of sample collection relative to the menstrual cycle.[3,19] Our study's absence of fatty liver assessment contributed to the lack of significant associations, as FGF21 is closely linked to hepatic lipid metabolism, which is an important limitation in interpreting the role of FGF21.

The impact of obesity on FGF21 levels in patients with and without PCOS is still a matter of debate. Several studies suggested that the increase in FGF21 levels is unrelated to PCOS and is proportional to BMI.[7] These studies also demonstrated positive correlations between FGF21 levels and body fat mass and its percentage, waist circumference, and HOMA-IR. In parallel, the relationship between obesity and FGF21 was explained by the increase in FGF21 expression in the visceral fat of obese individuals.[7,20] Along these lines, Gorar et al[11] suggested that increased FGF21 levels in patients with PCOS were associated with increased BMI values. In contrast, we, as Sahin et al[10] did not find a significant correlation between these variables. Sahin et al concluded that FGF21 was not a helpful marker for metabolic abnormalities, including insulin resistance, dyslipidemia, obesity, and hypertension in PCOS patients.[10]

The association between FGF21 and hormonal imbalances remains a subject of speculation.[7,10,11] Given that LH and androgens are central to the hormonal diagnostic criteria of PCOS, such possible associations suggest that FGF21 plays a role in the hormonal pathophysiology of the disorder, warranting further investigation.[1,2,11] Olszanecka-Glinianowicz et al[7] no association between elevated FGF21 levels and sex hormone disturbances in women with PCOS. Conversely, other studies have demonstrated positive correlations between FGF21 and LH or testosterone levels,[11] while a negative correlation between FGF21 and DHEA-S has also been observed.[10] Given that LH and testosterone are central to the hormonal diagnostic criteria of PCOS, these associations suggest that FGF21 may play a role in the hormonal pathophysiology of the disorder, warranting further investigation.[1,2,11] The correlation analysis in this study showed a statistically significant positive correlation between FGF21 and DHEAS in the entire study population, contrary to Sahin's study.[10] As an interesting finding, the degree of this correlation was relatively increased in all PCOS patients. However, lack of significance between FGF21 and DHEAS might indicate that the observed relationship may be linked explicitly to PCOS pathophysiology rather than obesity status alone. The positive correlation between FGF21 and DHEAS specifically in PCOS patients represents a novel finding within our study cohort that warrants consideration in the context of PCOS's complex endocrine and metabolic interactions. When stratifying by obesity status, the absence of significant correlations between FGF21 and hormonal parameters in the obese subgroup suggests differential regulatory mechanisms may be at play depending on the underlying pathophysiological condition.

The inconsistency between our findings and previous studies may reflect sample size constraints and differences in study populations. Specifically, the small number of participants in each subgroup (obese/non-obese PCOS and control groups) may have limited our statistical power to detect subtle but potentially meaningful differences. Furthermore, the unequal group sizes may have affected the robustness of intergroup comparisons. These conflicting findings may be attributed to the complex interplay between FGF21 and metabolic processes. Therefore, further studies are needed to elucidate the underlying pathophysiological mechanisms of PCOS. Future research should also consider stratification by liver fat content and other metabolic comorbidities to more accurately isolate the effects of FGF21.

Limitations of the Study

This study has several limitations worth mentioning. First, the relatively small sample size may have limited the generalizability of the findings. The limited number of participants in each may have exceptionally constrained the

detection of statistically significant differences in FGF21 levels between PCOS phenotypes and control groups. Therefore, more extensive cohort studies are needed to validate the findings. Secondly, considering the study's design and methodological variations, such as differences in diagnostic criteria for PCOS, sample size, and the assays used for FGF21 measurement, longitudinal studies may be more helpful in investigating the temporal relationships between FGF21 and PCOS. Thirdly, the potential impact of confounding factors, such as dietary habits, physical activity levels, and genetic predispositions, was not comprehensively evaluated. Lastly, the lack of advanced imaging techniques or liver biopsies to assess hepatic steatosis and fibrosis may have limited the ability to explore the role of FGF21 in hepatic manifestations of PCOS. Since FGF21 is known to increase in response to hepatic stress and steatosis, this omission may have obscured important underlying relationships. Addressing these limitations in future studies will provide a more comprehensive understanding of the role of FGF21 in PCOS.

Conclusions

In conclusion, FGF21 does not appear to play a significant role in the pathophysiology of PCOS or its associated metabolic abnormalities due to the lack of significant differences between women with PCOS and healthy controls, regardless of their obesity status. We found no significant correlation between FGF21 levels and key metabolic parameters, including age, BMI, waist circumference, body fat percentage, or HOMA-IR. However, the interpretation of these findings is limited by the small sample size, absence of hepatic steatosis assessment, and potential residual confounding. Additionally, the absence of data on hepatic steatosis—despite FGF21 being a recognized biomarker for fatty liver—may have led to an underestimation of its role in metabolically active PCOS phenotypes, particularly in obese patients So, these findings suggest that FGF21 may not serve as a distinct biomarker for PCOS independent of metabolic factors such as insulin resistance and body composition.

This study's findings will likely contribute to the growing evidence on FGF21 and its role in metabolic disorders. Future studies with a longitudinal design that includes more extensive and diverse populations and comprehensively evaluates metabolic and hormonal factors are needed to clarify the complex interactions between FGF21 and hyperandrogenism, obesity, and insulin resistance in PCOS.

Abbreviations

FGF21, Fibroblast Growth Factor 21; PCOS, Polycystic Ovary Syndrome; BMI, Body Mass Index; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein.

Data Sharing Statement

The datasets analyzed during this study are available from the corresponding author upon reasonable request and are subject to institutional review board approval.

Ethical Approval and Informed Consent

This study was approved by the Uludağ University Faculty of Medicine Ethics Committee on October 3, 2017 (Approval No: 2017-14/47). At the time of the study's application, Bursa Yüksek İhtisas Hospital did not have a local ethics committee. However, since both institutions are in the same province, agreements were in place to facilitate research at Bursa Yüksek İhtisas Hospital, ensuring compliance with ethical guidelines and oversight by the approved ethics committee. The study was conducted with the ethical considerations outlined in the Declaration of the Helsinki.

Written informed consent was obtained from all participants before enrollment in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, or interpretation. Derya Koçaslan designed the study, collected data, and drafted the manuscript. Gürcan Kısakol performed the statistical analysis and critically revised the manuscript. Both authors participated in drafting and reviewing the article, approved the final version to be published, agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

References

1. Garcia-Beltran C, Peyrou M, Navarro-Gascon A, et al. Organokines and liver enzymes in adolescent girls with polycystic ovary syndrome during randomized treatments. *Front Endocrinol*. 2024;15. doi:10.3389/FENDO.2024.1325230
2. Kahraman S, Altinova AE, Yalcin MM, et al. Association of serum betatrophin with fibroblast growth factor-21 in women with polycystic ovary syndrome. *J Endocrinol Invest*. 2018;41(9):1069–1074. doi:10.1007/S40618-018-0831-2
3. Yoost JL, Ruley M, Smith K, Santanam N, Cyphert HA. Diagnostic value of bile acids and fibroblast growth factor 21 in women with polycystic ovary syndrome. *Women's Health Reports*. 2022;3(1):803. doi:10.1089/WHR.2022.0060
4. Giannouli A, Stefanaki C, Kouskoutis C, et al. Hepatokine Profile in Adolescents with Polycystic Ovary Syndrome: a Case-Control Study. *J Clin Med*. 2023;12(17). doi:10.3390/JCM12175744
5. Białka-Kosiec A, Orszulak D, Gawlik A, Drosdzol–Cop A. The relationship between the level of vitamin D, leptin and FGF23 in girls and young women with polycystic ovary syndrome. *Front Endocrinol*. 2022;13. doi:10.3389/FENDO.2022.1000261
6. Gateva A, Tsakova A, Hristova J, Kamenov Z. Fibroblast growth factor 23 and 25(OH)D levels are related to abdominal obesity and cardiovascular risk in patients with polycystic ovarian syndrome. *Gynecol Endocrinol*. 2020;36(5):402–405. doi:10.1080/09513590.2019.1689550
7. Olszanecka-Glinianowicz M, Madej P, Wdowczyk M, Owczarek A, Chudek J. Circulating FGF21 levels are related to nutritional status and metabolic but not hormonal disturbances in polycystic ovary syndrome. *Eur J Endocrinol*. 2015;172(2):173–179. doi:10.1530/EJE-14-0539
8. Siemienowicz KJ, Furmanska K, Filis P, et al. Pubertal FGF21 deficit is central in the metabolic pathophysiology of an ovine model of polycystic ovary syndrome. *Mol Cell Endocrinol*. 2021;525:111196. doi:10.1016/J.MCE.2021.111196
9. Barb D, Bril F, Kalavalapalli S, Cusi K. Plasma fibroblast growth factor 21 is associated with severity of nonalcoholic steatohepatitis in patients with obesity and type 2 diabetes. *J Clin Endocrinol Metab*. 2019;104(8):3327–3336. doi:10.1210/JC.2018-02414
10. Sahin SB, Ayaz T, Cure MC, et al. Fibroblast growth factor 21 and its relation to metabolic parameters in women with polycystic ovary syndrome. *Scand J Clin Lab Invest*. 2014;74(6):465–469. doi:10.3109/00365513.2014.900821
11. Gorar S, Culha C, Alphan Uc Z, et al. Serum fibroblast growth factor 21 levels in polycystic ovary syndrome. *Gynecol Endocrinol*. 2010;26 (11):819–826. doi:10.3109/09513590.2010.487587
12. Fauser BCJM, Chang J, Legro R, et al. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod*. 2004;19(1):41–47. doi:10.1093/HUMREP/DEH098
13. Keskin M, Arsoy HA, Kara O, Sarandol E, Koca N, Yilmaz Y. Impact of comorbid polycystic ovary syndrome on clinical and laboratory parameters in female adolescents with metabolic dysfunction-associated steatotic liver disease: a cross-sectional study. *J Clin Med*. 2024;13 (19):5885. doi:10.3390/JCM13195885
14. Arpaci D, Gurkan Tocoglu A, Yilmaz S, et al. The relationship between epicardial fat tissue thickness and visceral adipose tissue in lean patients with polycystic ovary syndrome. *J Ovarian Res*. 2015;8(1):71. doi:10.1186/S13048-015-0197-4
15. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):499–502. doi:10.1093/CLINCHEM/18.6.499
16. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45(3):1–67. doi:10.18637/JSS.V045.I03
17. Ramanjaneya M, Bensila M, Bettahi I, et al. Dynamic changes in circulating endocrine FGF19 subfamily and Fetuin-A in response to intralipid and insulin infusions in healthy and PCOS women. *Front Endocrinol*. 2020:11. doi:10.3389/FENDO.2020.568500
18. Cheng F, Ng NYH, Tam CHT, et al. Association between FGF19, FGF21 and lipocalin-2, and diabetes progression in PCOS. *Endocr Connect*. 2021;10(10):1243–1252. doi:10.1530/EC-21-0082
19. Wang D, Zhu W, Li J, An C, Wang Z. Serum concentrations of fibroblast growth factors 19 and 21 in women with gestational diabetes mellitus: association with insulin resistance, adiponectin, and polycystic ovary syndrome history. *PLoS One*. 2013;8(11). doi:10.1371/JOURNAL.PONE.0081190
20. Mraz M, Bartlova M, Lacinova Z, et al. Serum concentrations and tissue expression of a novel endocrine regulator fibroblast growth factor-21 in patients with type 2 diabetes and obesity. *Clin Endocrinol*. 2009;71(3):369–375. doi:10.1111/J.1365-2265.2008.03502.X