Original Article

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Association of Circulating FGF-23 and Klotho with Cardiovascular Disease in Patients with Chronic Kidney Disease

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Abstract

Aim: Chronic kidney disease (CKD) contributes to an increased risk of cardiovascular disease (CVD) beyond traditional risk factors, partly through the fibroblast growth factor 23 (FGF-23) and Klotho pathways. This study examined the association between circulating FGF-23 and Klotho levels and CVD in individuals with CKD.

Methods: This cross-sectional study included 110 patients with CKD treated at University of Health Sciences Türkiye, Istanbul Haseki Training and Research Hospital. Patients were classified into CVD-positive (n=56) and CVD-negative (n=54) groups according to the presence of CVD, defined as coronary artery disease, ischaemic stroke, or peripheral arterial disease. Serum FGF-23 and Klotho levels were quantified using enzyme-linked immunosorbent assay, and routine biochemical and hormonal parameters were simultaneously assessed. Statistical analyses included group comparisons, correlation analyses, and binary logistic regression.

Results: Patients with CVD had higher serum FGF-23 levels than those without CVD (p=0.022), whereas Klotho levels did not differ between the groups. Multivariate regression analyses showed that FGF-23 was associated with CVD [odds ratio =1.0026 (1.0002-1.0049), p=0.032] after adjusting for estimated glomerular filtration rate, age, sex, diabetes mellitus, and hypertension. Klotho showed inverse correlations with creatinine (r=-0.297, p=0.029) in CVD-negative patients and with glucose (r=-0.299, p=0.025) in CVD-positive patients and was positively associated with FGF-23 (r=0.558, p<0.001) in CVD-positive patients.

Conclusion: Elevated FGF-23 levels were associated with CVD in patients with CKD, whereas Klotho levels did not distinguish patients with CVD. These findings suggest a possible relationship between FGF-23 and CVD in CKD; however, further studies are required.

Keywords: Cardiovascular disease, creatinine, enzyme-linked immunosorbent assay, fibroblast growth factor, renal insufficiency

Introduction

Chronic kidney disease (CKD) is a major global health problem and is projected to become the fifth leading cause of years of life lost by 2040, with cardiovascular disease (CVD) accounting for over half of the deaths in this population (1,2). The excess cardiovascular risk observed in patients with CKD cannot be fully explained by traditional risk factors, suggesting the involvement of disease-specific mechanisms (2,3). Disturbances in mineral metabolism are a central feature of CKD and play a critical role in the development of cardiovascular complications. In this context, the fibroblast growth factor 23 (FGF-23)-Klotho axis has emerged as a key pathway linking kidney dysfunction and cardiovascular pathology (4,5).

Fibroblast growth factor 23 levels increase early in the course of CKD, often preceding abnormalities in phosphate or parathyroid hormone levels, whereas Klotho expression progressively declines as kidney function deteriorates (5,6). Compared to Klotho, FGF-23 has been more extensively investigated, and accumulating evidence has linked elevated FGF-23 levels to adverse cardiovascular outcomes in CKD, particularly cardiac remodelling and left ventricular hypertrophy (7). Despite increasing evidence

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supporting the individual roles of FGF-23 and Klotho, data evaluating their combined association with established CVD in patients with CKD remain limited (8).

We hypothesised that circulating FGF-23 and Klotho levels are associated with CVD in patients with CKD and may serve as independent cardiovascular risk markers beyond traditional risk factors. This study aimed to investigate the relationship between FGF-23, Klotho, and CVD in patients with CKD.

Materials and Methods

Compliance with Ethical Standards

The study was conducted with approval of the University of Health Sciences Türkiye, Istanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 1448, date: 28.09.2018). Any personal or identifiable information was anonymised throughout the study to ensure confidentiality. The study was carried out in line with the ethical standards outlined in the Helsinki Declaration. Written informed consent was obtained from all the participants before their inclusion in the study.

Study Design and Patient Selection

We analysed 110 consecutive patients with CKD who were admitted to the Nephrology Clinic of University of Health Sciences Türkiye, Istanbul Haseki Training and Research Hospital between October 2018 and April 2019. In all cases, serum FGF-23 and Klotho levels were assessed simultaneously with routine biochemical and hormonal tests, such as creatinine, estimated glomerular filtration rate (eGFR), urea, calcium, magnesium, phosphorus, parathyroid hormone, glucose, and 25-hydroxyvitamin D. The eGFR was calculated using the CKD Epidemiology Collaboration equation. Clinical data for each patient, including cardiovascular status, smoking history, hypertension, diabetes mellitus, coronary artery disease, ischaemic stroke, and peripheral artery disease, were recorded. Cardiovascular disease was defined as the presence of coronary artery disease, ischaemic stroke, or peripheral arterial disease. Coronary artery disease was defined as a history of percutaneous coronary intervention (stent implantation) or coronary artery bypass grafting. Ischemic stroke was defined based on a diagnosis documented in the medical history and supported by imaging findings. Peripheral arterial disease was defined as a history of peripheral revascularisation or imaging-confirmed disease.

Laboratory Measurements

Routine biochemical and hormonal analyses were performed using an AU5800 analyser (Beckman Coulter, Brea, CA, USA) and a Siemens Immulite 1000 Immunoassay System (Siemens Healthcare Diagnostics, Los Angeles, CA, USA), respectively. Commercial enzyme-linked immunosorbent assay kits were used to assess serum FGF-23 and Klotho levels following the manufacturer's guidelines (Sunred Biological Technology Co. Ltd., Shanghai, China). The analytical sensitivity [limit of detection (LOD)] and measurement ranges of the assays were defined according to the manufacturer's specifications (catalogue numbers: FGF-23, 201-12-0060; Klotho, 201-12-2782). The LOD for FGF-23 was 5.147 pg/mL, with a measurement range of 10-1500 pg/mL. The LOD for Klotho was 0.05 ng/mL, with a measurement range of 0.1-20 ng/mL. The within-run coefficients of variation (CVs) for FGF-23 and Klotho were <10%, and the inter-assay CVs were <12%.

Individuals aged 18 years and above who were diagnosed with CKD, who were followed at the Nephrology Clinic of University of Health Sciences Türkiye, Istanbul Haseki Training and Research Hospital, and who had available serum FGF-23 and Klotho measurements and complete cardiovascular clinical data were included. Patients younger than 18 years; those diagnosed with acute kidney injury; those receiving kidney replacement therapy; those with a history of kidney transplantation; and those with active infection, inflammatory or autoimmune disease, malignancy, chronic liver disease, or an acute cardiovascular event within the previous three months were excluded (Figure 1).

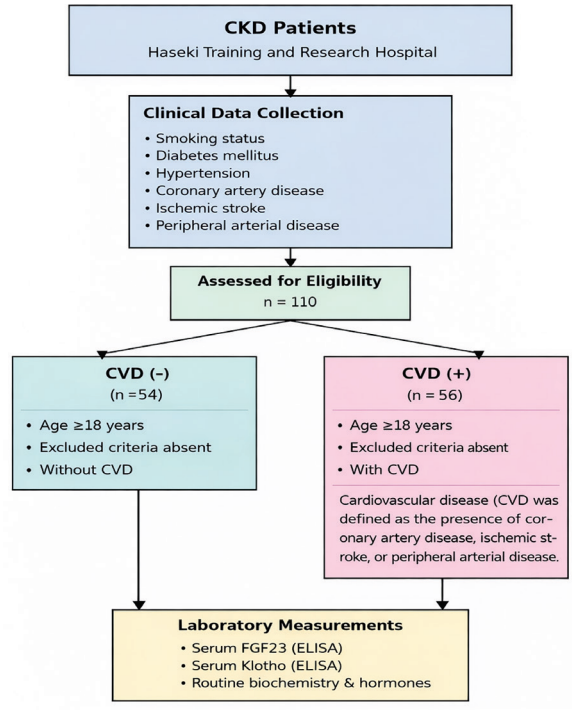

Figure 1. Flow diagram of the study population and participant selection

CKD: Chronic kidney disease, CVD: Cardiovascular disease, ELISA: Enzyme-linked immunosorbent assay, FGF-23: Fibroblast growth factor 23

Sample Size Estimation

The sample size was estimated a priori based on the expected difference in serum FGF-23 levels between patients with and without CVD. Using an effect size of Cohen's d=1.19 derived from the findings of Khodeir et al. (5), a two-sided alpha level of 0.05 and 95% power, the minimum required total sample size was calculated as 40 participants. To improve the precision of the estimates and account for potential exclusions or incomplete data, all 110 eligible patients were included in the analysis. The sample size calculation was performed using G*Power version 3.1.9.7 software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany).

Statistical Analysis

Statistical analyses were carried out using IBM SPSS v. 26 (Armonk, NY, USA) and GraphPad Prism v. 10.4.2 (San Diego, CA, USA). Normality of the data was assessed using the Kolmogorov-Smirnov test. Categorical variables were examined using the chi-square test or Fisher's exact test. Student's t-test was used for parametric data, and the Mann-Whitney U test was used for non-parametric data. The Kruskal-Wallis test was used to compare FGF-23 and Klotho levels among the three independent groups. Spearman's rank correlation analysis was conducted to explore the relationships between FGF-23, Klotho, and other variables. In the binary logistic regression model, the FGF-23 level was included as an independent variable, and the analysis was adjusted for eGFR, age, sex, diabetes mellitus, and hypertension to assess its association with the presence of CVD. Covariates were selected a priori based on their established clinical relevance and evidence from previous literature. Statistical significance was defined as $p<0.05$.

Results

Table 1 presents the demographic features of the CVD-positive and CVD-negative groups. The groups did not differ significantly with respect to age, sex, smoking status, or hypertension prevalence ($p>0.05$). However, the CVD-positive group exhibited significantly higher incidence rates of diabetes mellitus ($p=0.022$), coronary artery disease ($p<0.001$), ischaemic stroke ($p=0.027$), and peripheral arterial disease ($p=0.027$) compared with the CVD-negative group (Table 1).

Table 2 presents the results of the between-group statistical analyses of FGF-23, Klotho, and other biochemical variables evaluated in the study. Fibroblast growth factor 23 levels were elevated in the CVD-positive group [130 (38.7-231)] compared to the CVD-negative group [69.9 (33.6-141)], with a p-value of 0.022 (Figure 2). The groups did not differ significantly with respect to levels of Klotho, creatinine, urea, calcium, phosphorus, magnesium, parathyroid hormone, and 25-hydroxyvitamin D. Additionally, glucose levels were higher in the CVD-positive group [139 (109-186)] than in the CVD-negative group [108 (96.0-136)]; $p=0.002$ (Table 2).

Table 1. Baseline characteristics of the CVD (+) and CVD (-) groups

Variables	CVD (-) (n=54)	CVD (+) (n=56)	p-value
Age (years), mean ± SD	64.2±9.02	67.4±8.24	0.054[a]
Gender, n (%) Female Male	 23 (42.6) 31 (57.4)	 19 (33.9) 37 (66.1)	0.350[b]
Smoking status, n (%) No Yes	 36 (66.7) 18 (33.3)	 36 (64.3) 20 (35.7)	0.951[b]
Diabetes mellitus, n (%) No Yes	 29 (53.7) 25 (46.3)	 17 (30.4) 39 (69.6)	**0.022[b]**
Hypertension, n (%) No Yes	 7 (13.0) 47 (87.0)	 5 (8.90) 51 (91.1)	0.709[b]
Coronary artery disease, n (%) No Yes	 54 (100) 0 (0.00)	 4 (7.10) 52 (92.9)	**<0.001[b]**
Ischemic stroke, n (%) No Yes	 54 (100) 0 (0.00)	 50 (89.3) 6 (10.7)	**0.027[b]**
Peripheral arterial disease, n (%) No Yes	 54 (100) 0 (0.00)	 50 (89.3) 6 (10.7)	**0.027[b]**

Statistically significant values ($p<0.05$) are shown in bold. [a]Student's t-test, [b]Chi-square
CVD: Cardiovascular disease, SD: Standard deviation

Table 2. Laboratory parameters of the CVD (+) and CVD (-) groups			
Variables	**CVD (-) (n=54)**	**CVD (+) (n=56)**	**p-value**
FGF-23 (pg/mL), median (25^{th}-75^{th} percentiles)	69.9 (33.6-141)	130 (38.7-231)	**0.022[a]**
Klotho (ng/mL), median (25^{th}-75^{th} percentiles)	4.00 (3.34-4.90)	4.29 (3.54-6.23)	0.149[a]
Creatinine (mg/dL), median (25^{th}-75^{th} percentiles)	1.80 (1.46-2.60)	1.89 (1.41-2.54)	0.902[a]
eGFR (mL/min/1.73 m^2), mean ± SD	32.4±12.9	34.4±14.5	0.450[b]
Urea (mg/dL), median (25^{th}-75^{th} percentiles)	77.7 (58.0-94.5)	68.2 (49.0-106)	0.403[a]
Calcium (mg/dL), median (25^{th}-75^{th} percentiles)	9.70 (9.40-10.0)	9.60 (9.10-9.95)	0.410[a]
Phosphorus (mg/dL), mean ± SD	3.87±0.63	3.76±0.92	0.441[b]
Magnesium (mg/dL), mean ± SD	2.11±0.38	2.06±0.35	0.424[b]
Glucose (mg/dL), median (25^{th}-75^{th} percentiles)	108 (96.0-136)	139 (109-186)	**0.002[a]**
25(OH)D (ng/mL), median (25^{th}-75^{th} percentiles)	16.9 (11.6-24.8)	14.8 (10.3-24.2)	0.453[a]
PTH (pg/mL), median (25^{th}-75^{th} percentiles)	94.0 (67.0-149)	122 (61.0-188)	0.212[a]

Statistically significant values (p<0.05) are shown in bold. Variables with a normal distribution were expressed as mean ± standard deviation, while variables without a normal distribution were expressed as median (25^{th}-75^{th} percentiles). [a]Mann-Whitney U test, [b]Student's t-test
FGF-23: Fibroblast growth factor 23, eGFR: Estimated glomerular filtration rate, 25(OH)D: 25-hydroxyvitamin D, PTH: Parathyroid hormone, CVD: Cardiovascular disease, SD: Standard deviation

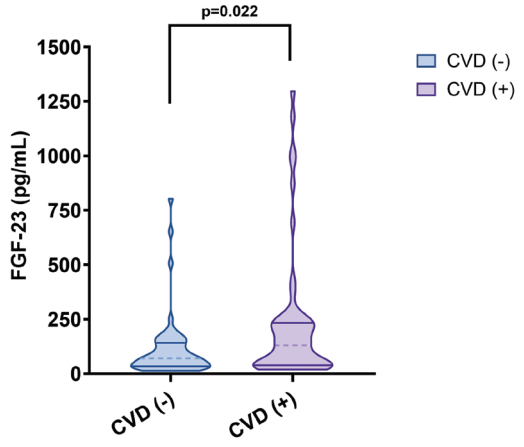

Figure 2. Comparison of FGF-23 levels in patients categorized by cardiovascular disease status
CVD: Cardiovascular disease, FGF-23: Fibroblast growth factor 23

In the univariate regression analysis, FGF-23 demonstrated a significant association with the presence of CVD [odds ratio (OR)=1.0024 (1.0002-1.0047), p=0.035]. In the multivariate regression model, FGF-23 was associated with CVD [OR=1.0026 (1.0002-1.0049), p=0.032] after adjusting for eGFR, age, sex, diabetes mellitus, and hypertension (Table 3).

Fibroblast growth factor 23 levels were positively correlated with Klotho levels in the CVD-positive group (r=0.558, p<0.001). Conversely, Klotho levels were negatively correlated with creatinine levels (r=-0.297, p=0.029) in the CVD-negative group. Additionally, Klotho levels were negatively correlated with glucose levels (r=-0.299, p=0.025) in the CVD-positive group (Table 4).

Patients were categorised into three groups based on eGFR levels, corresponding to CKD stages: 45-59 (n=27), 30-44 (n=35), and <30 (n=48) mL/min/1.73 m^2. Fibroblast growth factor 23 levels were not significantly different among the groups (p=0.496), with median (25^{th}-75^{th} percentile) values of 71.9 (25.3-167), 90.9 (57.5-185), and 106 (34.2-191), respectively. Similarly, Klotho levels did not differ significantly among the groups (p=0.999); median (25^{th}-75^{th} percentiles) values were 4.28 (3.30-5.82), 4.28 (3.29-6.34), and 4.11 (3.60-5.58), respectively.

Discussion

This study assessed the relationship of circulating FGF-23 and Klotho with the occurrence of CVD in patients with CKD. Our findings indicated that FGF-23 was significantly higher in the CVD-positive group and remained independently associated with CVD after controlling for traditional cardiovascular risk factors. Conversely, serum Klotho levels did not differ significantly between patients with and without CVD. These findings are consistent with previous studies suggesting an association between FGF-23 and cardiovascular risk (9-11).

The study groups were demographically similar; no notable differences in age, sex, smoking habits, or hypertension were observed between groups. The higher prevalence of diabetes mellitus and atherosclerotic cardiovascular conditions in patients with CVD is consistent with epidemiological data in CKD populations and aligns with previously reported findings (2). The similar distribution of traditional risk factors supports the notion that the observed association between FGF-23 and CVD is not solely attributable to baseline clinical differences.

Table 3. Binary logistic regression analysis results for effects of FGF-23 on cardiovascular disease				
Variables	**Univariate**		**Multivariate***	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
FGF-23 (pg/mL)	1.0024 (1.0002-1.0047)	**0.035**	1.0026 (1.0002-1.0049)	**0.032**

Statistically significant values (p<0.05) are shown in bold
*Adjusted for eGFR, hypertension, diabetes mellitus, age, and sex.
CI: Confidence interval, OR: Odds ratio, eGFR: Estimated glomerular filtration rate, FGF-23: Fibroblast growth factor 23

Table 4. Correlations between FGF-23 and Klotho and other variables								
Parameter	**FGF-23 (pg/mL)**				**Klotho (ng/mL)**			
	CVD (-) (n=54)		**CVD (+) (n=56)**		**CVD (-) (n=54)**		**CVD (+) (n=56)**	
	r	**p-value**	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**
Klotho (ng/mL)	0.248	0.071	**0.558**	**<0.001**	1.000	<0.001	1.000	<0.001
Creatinine (mg/dL)	0.076	0.583	-0.063	0.643	**-0.297**	**0.029**	0.111	0.413
eGFR (mL/min/1.73 m²)	-0.123	0.377	0.049	0.722	0.216	0.117	-0.136	0.319
Urea (mg/dL)	0.054	0.699	-0.039	0.774	-0.162	0.243	0.111	0.417
Calcium (mg/dL)	-0.027	0.844	-0.127	0.349	-0.001	0.995	-0.088	0.520
Phosphorus (mg/dL)	-0.133	0.337	-0.049	0.718	0.093	0.502	0.114	0.404
Magnesium (mg/dL)	0.112	0.421	0.101	0.458	-0.098	0.480	0.127	0.353
Glucose (mg/dL)	-0.106	0.446	-0.191	0.157	-0.115	0.406	**-0.299**	**0.025**
25(OH)D (ng/mL)	0.155	0.264	0.026	0.848	-0.090	0.518	-0.157	0.249
PTH (pg/mL)	0.011	0.935	-0.172	0.206	-0.039	0.777	-0.054	0.695

Statistically significant values (p<0.05) are shown in bold
FGF-23: Fibroblast growth factor 23, eGFR: Estimated glomerular filtration rate, 25(OH)D: 25-hydroxyvitamin D, PTH: Parathyroid hormone, CVD: Cardiovascular disease

Elevated FGF-23 levels in patients with CVD represent a central finding of this study. This observation is in agreement with large cohort studies and meta-analyses demonstrating that increased FGF-23 concentrations are associated with heart failure, left ventricular hypertrophy, cardiovascular events, and mortality across different CKD stages (10,11).

The groups did not differ significantly in kidney function parameters and traditional markers of mineral metabolism. This finding indicates that the association between FGF-23 and CVD cannot be attributed solely to advanced renal dysfunction or pronounced disturbances in mineral metabolism. Previous studies have similarly demonstrated that FGF-23 is associated with cardiovascular risk independently of serum phosphate and parathyroid hormone levels (9,10).

In contrast to FGF-23 levels, serum Klotho levels were not significantly different between patients with and without CVD. This observation aligns with findings from cross-sectional studies highlighting the limited discriminatory capacity of Klotho for established CVD. Data from the chronic renal insufficiency cohort study (12) indicated that circulating Klotho levels were not correlated with mortality, hospitalisation due to heart failure, atherosclerotic cardiovascular events, or the progression of kidney disease in patients with CKD. Furthermore, Klotho deficiency did not confound or alter the association between FGF-23 and adverse clinical outcomes. These results imply that circulating Klotho may play a limited role in determining short- to mid-term clinical outcomes in CKD (12). Consistent with these findings, serum Klotho levels in the present study did not differ between patients with and without established CVD and did not independently discriminate CVD status. In contrast, FGF-23 levels appeared to be independently associated with CVD. Overall, these results show that FGF-23 is more closely linked to cardiovascular risk than circulating Klotho levels in people with CKD.

Multivariate analysis showed an association between FGF-23 and CVD after adjusting for eGFR, age, sex, diabetes mellitus, and hypertension. Although the effect size per unit increase appeared modest, the wide biological range of FGF-23 levels observed in patients with CKD suggests that cumulative increases may have clinically meaningful implications. Previous studies have reported dose-dependent and nonlinear associations between FGF-23 levels and adverse cardiovascular outcomes, particularly at high concentrations (10,13).

In this study, the moderate and statistically significant positive correlation observed between FGF-23 and Klotho in the CVD-positive group (r=0.558, p<0.001) suggests

that the FGF-23–Klotho axis may exhibit a different regulatory pattern in the presence of CVD. Although FGF-23 and Klotho are classically considered to have an inverse physiological relationship, previous studies have reported inconsistent associations between these biomarkers in CKD (7,12). In addition, circulating soluble Klotho does not necessarily reflect tissue-level expression or biological activity (14,15), which may partly explain the unexpected findings. Furthermore, both FGF-23 and Klotho may be influenced by shared pathophysiological processes in CKD and CVD, potentially leading to parallel changes under certain conditions (8). Therefore, the positive correlation observed in our study may reflect disease-specific regulatory mechanisms rather than direct physiological interactions. The absence of a significant association in the CVD-negative group indicates that this parallel increase may be specific to the disease context. Additionally, the inverse relationships observed between Klotho levels and creatinine and glucose levels support previous findings linking reduced Klotho availability to declining renal function and metabolic dysregulation (7,12). Although FGF-23 and Klotho are known to constitute a closely related physiological axis, the observed correlation should not be interpreted as evidence of a causal relationship and may be influenced by concomitant renal function, metabolic status, or other regulatory factors.

In this context, the positive correlation observed between FGF-23 and Klotho in the CVD-positive group may reflect a combination of compensatory Klotho upregulation, functional Klotho resistance, chronic cardiovascular stress, increased Klotho shedding, and disease-specific regulatory mechanisms. This finding does not indicate preservation of the physiological FGF-23-Klotho balance; rather, it emphasises the complex nature of this axis in established CVD and highlights the limitations of interpreting circulating biomarkers in isolation (16-19).

Although the per-unit effect size of FGF-23 was modest, its wide biological range and previously demonstrated nonlinear and dose-dependent associations with cardiovascular outcomes suggest that even small increases may be clinically meaningful (9,20-22). As reported in previous studies, potential variability in biomarker measurements should be considered when interpreting these findings (9,12,15). Cardiovascular disease was defined by imaging and documented diagnoses, including coronary artery disease, peripheral arterial disease, and stroke; however, subclinical disease could not be excluded.

Overall, our findings are consistent with accumulating evidence that FGF-23 plays a role in CKD-associated CVD and is independently associated with cardiovascular risk beyond traditional factors (23,24). FGF-23 may represent a potential biomarker for cardiovascular risk stratification in patients with CKD; however, prospective studies are required before routine clinical application.

Study Limitations

This study has several limitations. First, its cross-sectional, single-centre design limits the ability to establish causality between FGF-23 levels and CVD and may restrict the generalisability of the findings. Therefore, the observed associations should be interpreted as correlational, and prospective longitudinal multicentre studies are needed to clarify potential causal relationships. Second, the relatively modest sample size may have limited our ability to detect subtle associations, particularly those involving serum Klotho levels. Third, CVD was identified based on clinical history and medical records, which does not permit the exclusion of subclinical disease. Furthermore, serum Klotho levels may not accurately reflect tissue-level Klotho expression or biological activity, which may partially explain the lack of an observed association between Klotho levels and CVD. Additionally, urinary albumin-to-creatinine ratio data were unavailable for all patients and were therefore excluded from the analysis, which may have limited the clinical interpretation of our findings.

Despite these limitations, this study is among recent investigations highlighting CVDs associated with CKD. In addition, the comprehensive evaluation of a wide range of biochemical parameters, together with analyses stratified by disease stage, constitutes a significant strength of the study. Moreover, the simultaneous evaluation of FGF-23 and Klotho in this patient population constitutes an additional strength, as studies assessing both biomarkers together in this group are limited.

Conclusion

Based on these findings, this study demonstrates that circulating FGF-23 levels are significantly associated with CVD in individuals with CKD, whereas serum Klotho levels do not differ by CVD status. Our findings indicate a possible association between FGF-23 and cardiovascular risk in CKD, which requires further confirmation.

Ethics

Ethics Committee Approval: The study was conducted with the approval University of Health Sciences Türkiye, Istanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 1448, date: 28.09.2018).

Informed Consent: Written informed consent was obtained from all the participants before their inclusion in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.Y., L.D., Concept: A.Y., L.D., Design: A.Y., L.D., Data Collection or Processing: A.Y., L.D., Analysis or Interpretation: A.Y., L.D., Literature Search: A.Y., L.D., Writing: A.Y., L.D.

Conflict of Interest: The authors declared that there were no conflicts of interest.

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