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Association of Fibroblast Growth Factor-23 with C-Reactive Protein, Serum Phosphate, and Bone Mineral Density in Chronic Kidney Disease

Dr. Ambreen Gul[1], Dr. Shabina Saifullah[2], Dr. Shahab Ullah[3], Dr. Summeira Jabeen Shah[4], Dr. Zakia Rehman[5], Dr. Chaman Gul[6*]

[1]Associate Professor Department of Chemical Pathology, Peshawar Medical College, Riphah International University, Islamabad
[2]Assistant Professor Department of Chemical Pathology, Peshawar Medical College, Riphah International University Islamabad
[3]Senior Lecturer, Department of Physiology, Jinnah Medical College, Peshawar
[4]Assistant Professor, Department of Biochemistry, Pak International Medical College, Peshawar
[5]Senior Demonstrator, Department of Biochemistry, Nust School of Health Sciences, NUST
[6]Associate Professor Department of Biochemistry, Bacha Khan Medical College, Mardan

***Corresponding Author:** Dr. Chaman Gul
Associate Professor Department of Biochemistry, Bacha Khan Medical College, Mardan
Email: chamangul72@yahoo.com

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ABSTRACT

Background: Chronic kidney disease (CKD) disrupts mineral metabolism and is associated with increased levels of 'Fibroblast Growth Factor-23' (FGF-23), a main 'regulator of phosphate homeostasis'. FGF-23 levels have been linked to inflammation, 'serum phosphate' dysregulation, and 'bone mineral density' (BMD) abnormalities. Understanding these relationships is essential for improving outcomes in 'CKD patients'. The objective was to assess the association of FGF-23 with C-reactive protein (CRP), serum phosphate, and BMD in patients with CKD.

Methodology

A cross-sectional study was conducted on CKD patients at Bacha Khan Medical College Mardan, examining FGF-23, CRP, serum phosphate, and BMD. Inclusion criteria were patients aged 18–65 years with stage 3–5 CKD. Exclusion criteria included patients with acute infections, recent fractures, or malignancies. Serum levels of FGF-23, phosphate, and CRP were measured, while BMD was assessed using dual-energy X-ray absorptiometry (DEXA). Data were analyzed using SPSS software.

Results

The study involved 200 participants. FGF-23 'levels were significantly correlated with CRP' (p less than 0.01) and serum phosphate (p less than 0.01). Patients with higher FGF-23 levels had lower BMD ($p < 0.05$). 'Multivariate regression analysis' showed that FGF-23 'was an independent predictor' of inflammation and bone mineral abnormalities in CKD patients.

Conclusion

FGF-23 is strongly associated with inflammation, phosphate dysregulation, and reduced bone mineral density in CKD patients. Addressing FGF-23 levels may offer therapeutic potential in mitigating the complications associated with CKD.

Keywords: Chronic kidney disease, CKD, inflammation, abnormalities

Introduction

The progressive disease known as 'Chronic kidney disease (CKD)' is characterized by impaired renal function, leading to systemic complications such as electrolyte imbalances, cardiovascular disease, and mineral bone disorders [1 2]. Among the numerous biochemical disturbances observed in CKD, elevated levels of Fibroblast Growth Factor-23 (FGF-23) have garnered significant attention. FGF-23, a hormone primarily secreted by osteocytes, plays a crucial 'role in regulating phosphate homeostasis and vitamin D metabolism' [3 4]. As CKD progresses, FGF-23 levels rise, reflecting the body's effort to maintain phosphate balance, despite declining renal function [5].

The elevated levels of FGF-23 seen in CKD are of particular concern due to their association with adverse outcomes [6]. Studies suggest that FGF-23 may serve as both a marker and a mediator of CKD progression. Elevated FGF-23 has been linked to increased mortality, particularly from 'cardiovascular disease, a leading cause of death in CKD patients' [7-9]. Additionally, FGF-23 has been shown to disrupt calcium-phosphate metabolism, contributing to secondary hyperparathyroidism and bone disorders, such as renal osteodystrophy [10 11].

'Inflammation, as evidenced by elevated levels of C-reactive protein (CRP)', is another significant feature of CKD. Chronic inflammation in CKD contributes to atherosclerosis, accelerated kidney function decline, and bone mineral loss [12]. There is growing evidence that FGF-23 and inflammation may be interconnected, with elevated FGF-23 levels correlating with higher CRP levels [13]. This suggests that FGF-23 may not only be a consequence of phosphate imbalance but also an active participant in the inflammatory processes that exacerbate CKD progression.

Phosphate dysregulation is another hallmark of CKD, particularly in later stages. As kidney function declines, phosphate excretion is impaired, leading to hyperphosphatemia [14]. This, in turn, stimulates increased FGF-23 secretion, creating a vicious cycle where both hyperphosphatemia and elevated FGF-23 contribute to further renal and cardiovascular damage. High phosphate levels have also been linked to vascular calcification, a significant contributor to cardiovascular morbidity and mortality in CKD [15].

Bone health in CKD is significantly impacted by mineral metabolism disturbances. Reduced Bone Mineral Density (BMD) is common in CKD patients, increasing the risk of fractures. FGF-23, through its suppression of active vitamin D and promotion of secondary hyperparathyroidism, contributes to bone mineral abnormalities [16]. CKD-related bone disease, or renal osteodystrophy, includes a spectrum of conditions that range from high bone turnover disorders to adynamic bone disease, all of which are influenced by dysregulated FGF-23 levels [17] .

Given the complex interplay between FGF-23, inflammation, phosphate homeostasis, and bone mineral metabolism, this study aims to explore these relationships in greater detail. By understanding the associations between FGF-23, CRP, serum phosphate, and BMD, we hope to elucidate potential therapeutic targets that could mitigate the systemic complications of CKD.

Methodology

This cross-sectional study was conducted at Bacha Khan Medical College Mardan. The study aimed to explore the associations between FGF-23, CRP, serum phosphate, and BMD in CKD patients. Ethical approval was obtained from the institutional review board, and informed consent was taken from all participants.

The study included 200 CKD patients aged 18–65 years, diagnosed with stage 3–5 CKD. Patients with acute infections, recent fractures, malignancies, or 'on medications affecting bone metabolism were excluded from the study'. A sample size calculation, based on a power of 80% and an alpha of 0.05, determined that 200 participants would be required to detect significant correlations between FGF-23, CRP, serum phosphate, and BMD.

Data were collected through clinical examinations, laboratory measurements, and imaging studies. 'FGF-23 levels were measured using enzyme-linked immunosorbent assay' (ELISA). Serum phosphate and CRP levels were assessed via standard biochemical methods. BMD was measured using dual-energy X-ray absorptiometry (DEXA) at the lumbar spine and femoral neck. Patients' demographic details, medical history, and CKD stage were recorded.

Data were analyzed using SPSS version 25. Descriptive statistics were used to summarize patient characteristics. Pearson's correlation coefficient was employed to assess the relationships between FGF-23, CRP, serum phosphate, and BMD. 'Multivariate regression analysis was used to determine the independent predictors of inflammation and bone mineral abnormalities'. 'A p-value of <0.05 was considered statistically significant'.

Results

Table 1, mean age was 52.3 ‘years’, with a ‘standard deviation (SD)’ of 10.6, indicating a moderately wide ‘age distribution’ between 18 and 65‘years. The mean FGF-23 level was 323.5 pg/mL, showing a variation of 50.2 pg/mL across participants, with levels ranging from 120 to 450 pg/mL. Serum phosphate levels had a mean of 5.2 mg/dL (SD 1.1), with a range of 3.1 to 8.5 mg/dL. Inflammatory marker C-reactive protein (CRP) showed elevated values, with a mean of 18.3 mg/L, suggesting a generally inflammatory profile in participants. The bone mineral density (BMD) values were relatively low, with a mean of 0.75 g/cm² (SD 0.10), indicating a potential risk for bone disorders in this population. Table 1.

Table 1: characteristics of study

‘Variable’	**‘Mean ± SD’**	**‘Range’**
Age (years)	52.3 ± 10.6	18-65
FGF-23 (pg/mL)	323.5 ± 50.2	120-450
Serum Phosphate (mg/dL)	5.2 ± 1.1	3.1-8.5
CRP (mg/L)	18.3 ± 6.5	5-30
BMD (g/cm²)	0.75 ± 0.10	0.50-1.10

The table 2 presents the correlations between FGF-23 and other parameters. A ‘significant’ association (r = 0.45, p less than 0.01) ‘was observed among FGF-23 And CRP’, indicating that ‘higher levels of FGF-23 were associated with increased inflammation in the participants’. ‘Similarly, FGF-23 was positively correlated with serum phosphate’ ($r = 0.50$, $p < 0.01$), suggesting that as FGF-23 increases, serum phosphate levels also rise. Contrariwise, a ‘negative correlation was found between FGF-23 and BMD’ ($r = -0.38$, $p < 0.05$), implying that elevated FGF-23 levels are linked with lower bone mineral density, which could contribute to bone weakening or osteoporosis in CKD patients.

Table 2: Correlation between FGF-23 and Study Variables

Variable	**Pearson’s r**	**p-value**
CRP	0.45	<0.01
Serum Phosphate	0.50	<0.01
BMD	-0.38	<0.05

The table 3 regression analysis for predictors of CRP (an inflammatory marker) showed that FGF-23 had the strongest predictive value ($\beta = 0.32$, $p < 0.01$), indicating that ‘higher FGF-23 levels’ were significantly ‘associated with increased inflammation, independent of other variables’. Serum phosphate ‘was also a significant predictor of CRP’ ($\beta = 0.25$, p ‘less than 0.05), further supporting the relationship between phosphate dysregulation and inflammation. Age, while showing a positive association ($\beta = 0.12$), ‘did not reach statistical significance’ ($p = 0.07$), suggesting that age may not be a strong independent predictor of CRP.

Table 3: ‘Multivariate regression’ analysis for identifying predictors of C-reactive protein (CRP)

Variable	**Coefficient (β)**	**p-value**
FGF-23	0.32	<0.01
Serum Phosphate	0.25	<0.05
Age	0.12	0.07

#In this regression analysis, FGF-23 was the strongest negative predictor of bone mineral density (BMD), with a coefficient of -0.40 ($p < 0.01$). This suggests that elevated levels of FGF-23 are associated with a significant reduction in BMD, highlighting a detrimental effect on bone health in CKD patients. Serum phosphate also negatively impacted BMD ($\beta = -0.30$, p less than 0.05), indicating that higher phosphate levels are associated with lower BMD, possibly due to secondary hyperparathyroidism or phosphate-related bone disease. Age was marginally associated with BMD ($\beta = -0.15$), but did not reach statistical significance ($p = 0.06$), though older age is often linked with bone loss. 'Table 4'

Table 4: Multivariate Regression Analysis for Predictors of BMD

Variable	Coefficient (β)	p-value
FGF-23	-0.40	<0.01
Serum Phosphate	-0.30	<0.05
Age	-0.15	0.06

Discussion

This study found a strong association between FGF-23 and CRP, serum phosphate, and BMD in CKD patients, underscoring the multifactorial role of FGF-23 in disease progression. The elevated levels of FGF-23 observed in CKD patients contribute to phosphate dysregulation, inflammation, and bone mineral loss, all of which are critical complications in the management of CKD.

The positive correlation between FGF-23 and CRP is accordance with studies that had observed a link 'between' FGF-23 and inflammatory markers in CKD patients [18]. Recently, a study by Dastghaib et al. (2023) highlighted that FGF-23 promotes inflammation through direct effects on immune cells [19]. This finding suggests that elevated FGF-23 may not merely be a marker of phosphate imbalance but an active participant in the inflammatory processes that drive CKD progression.

In contrast to these findings, some studies have suggested that FGF-23 levels are primarily driven by phosphate load rather than inflammation [20]. A study by Schlieper et al. (2022) argued that FGF-23 secretion is predominantly stimulated by hyperphosphatemia, with only indirect effects on inflammation [21]. However, the current study supports the notion that FGF-23 independently contributes to inflammation, even after adjusting for serum phosphate levels [22].

The association between FGF-23 and bone mineral density in CKD patients is also noteworthy. Elevated FGF-23 levels contribute to bone mineral loss through mechanisms such as reduced vitamin D activation and secondary hyperparathyroidism. Our findings align with those of Bilha et al. (2023), who 'reported that high FGF-23 levels were associated with lower BMD in CKD patients' [22] [23]. This suggests that targeting FGF-23 could potentially mitigate bone mineral disorders in this population.

One limitation of this study is the cross-sectional design, which precludes establishing causality. Longitudinal studies are needed to determine whether reducing FGF-23 levels can improve inflammation and bone health in CKD patients. Additionally, the study population consisted primarily of stage 3–5 CKD patients, limiting the generalizability of the findings to early-stage CKD or patients on dialysis.

Conclusion

The study demonstrates that elevated FGF-23 levels are associated with increased inflammation, phosphate dysregulation, and reduced bone mineral density in CKD patients. FGF-23 emerges as an important biomarker and potential therapeutic target for addressing systemic complications in CKD. Further longitudinal research is needed to explore the long-term benefits of modulating FGF-23 in CKD management.

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