International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Fibroblast Growth Factor 23 and Risk of Vascular Calcification in Hemodialysis Patients

Hala A. Mahmoud[1], Raghda G. Mostafa[1], Abdallah Mahmoud El-Ebidi[2], Ahmed H. Ahmed[3], Mohamed G. Saadi [4]*

[1*]*Department of Internal Medicine, Faculty of Medicine, Aswan University, Aswan, Egypt*
[1]*Department of Internal Medicine and Nephrology, Faculty of Medicine, Aswan University, Aswan, Egypt*
[2]*Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Aswan University, Aswan, Egypt*
[3]*Department of Diagnostic Radiology, Faculty of Medicine, Aswan University, Aswan, Egypt*
[4]*Department of Internal Medicine and Nephrology, Faculty of Medicine, Cairo University, Cairo, Egypt*

Abstract

The major cause of death in chronic kidney disease patients is cardiovascular disease. Although traditional risk factors (smoking, dyslipidemia, and diabetes mellitus) contribute to the development of cases, they cannot fully explain the unacceptably high incidence of mortality. This study aimed to assess the clinical correlation of FGF23, other bone mineral metabolism markers, and abdominal aortic calcification. In this case-control hospital-based study, 48 patients with end-stage renal disease on hemodialysis were randomly selected from the Dialysis Unit at Aswan University Hospital, and 48 age and sex-matched healthy control subjects. It was found that patients had significantly higher brachial PP, eGFR, and serum creatinine, phosphate, PTH, and FGF23 levels than in controls. Meanwhile, the patients with calcification had significantly higher BMI and serum levels of PTH and FGF23 than patients without any calcifications. In addition, there was a statistically positive significant correlation between serum FGF23 levels and AAC scores in patients. In addition, there were statistically significant positive correlations between serum FGF23 levels with BMI and serum PTH levels in the HD group. In the multivariable regression analysis, the presence of aortic calcification was independently associated with higher FGF-23, and it was the only significant explanatory and predictor variable for AAC among hemodialysis patients in the multivariable regression analysis adjusted other confounders. FGF-23 could be used as a potent predictor of vascular calcification among cases with hemodialysis.

Keywords: FGF-23, Chronic Kidney Disease, Haemodialysis, Vascular Calcification

Full length article **Corresponding Author*, e-mail: abdallahelebidi@aswu.edu.eg

1. Introduction

The major cause of death in chronic kidney disease (CKD) patients is cardiovascular disease (CVD) [1]. Although traditional risk factors (smoking, dyslipidemia, and diabetes mellitus) contribute to the development of CVD in CKD patients, they cannot fully explain the unacceptably high incidence of CV mortality [2]. Recently, non-traditional risk factors, including abnormal mineral metabolism, have been suggested to be involved in the increased risk of CV events [3-4]. One of the complications of CKD is CKD-mineral and bone disorder (CKD-MBD), which is defined as a clinical syndrome consisting of mineral, bone, and calcified CVDs according to The Kidney Disease Improving Global Outcomes [5]. The medical treatment of CKD-MBD has been associated with improvement in CVD complications and patient survival. A better understanding of the biomarkers and mechanisms involved in left ventricular hypertrophy (LVH) and vascular calcifications (VC) might improve the diagnosis and treatment of the CVD secondary to CKD-MBD, thus improving patient survival. Recent insights into fibroblast growth factor 23 (FGF23) and its co-receptor, Klotho, have led to marked advancements in the interpretation of data about CKD-MBD and CV damage [6-8]. Clinical studies in haemodialysis (HD) indicate a correlation of higher FGF23 levels and increased aortic calcification score, as assessed by multi-slice, spiral-computed tomography (CT) [9-10]. The key role of endocrine hormone FGF23 is to maintain phosphate homeostasis. It is secreted by osteocytes and osteoblasts in response to oral phosphate loading and parathyroid hormone (PTH) levels [11-12]. In the kidney,

physiological functions of FGF23 are mediated via binding to a complex of fibroblasts growth factor receptors (FGFRs) and its specific co-receptor Klotho [13]. Activation of the FGFR1–Klotho complex inhibits the expression and activity of the type II sodium-dependent phosphate transporters NaPi-2a and NaPi-2c, and thereby promotes renal phosphate excretion. Thus, with CKD progression, excess biologically active FGF23 is thought to occur in response to hyperphosphatemia ceases to be protective and may lead to pathological off-target effects that potentially contribute to the increase in mortality. Interventions that lower serum phosphate, such as oral phosphate binders to prevent intestinal absorption or possibly long-acting PTH analogs that reduce NPT2a or NPT2c expression may help prevent CKD-related FGF23 increases [14]. The current study aimed to assess the clinical correlation of FGF23, other bone mineral metabolism (BMM) markers (serum PTH, calcium, and phosphorus), and abdominal aortic calcification (AAC) as the risk of vascular calcification among haemodialysis patients.

2. Materials and Methods

In this case-control hospital-based study, a total of 48 patients with end-stage renal disease on hemodialysis were randomly selected from the Dialysis Unit at Aswan University Hospital, and 48 age and sex-matched healthy control subjects in the period from January 2021 to December 2022 were recruited. Using epi-info-7 to calculate sample size with the following assumptions: a case-control study, 80% power, 95% significance level: 0.4% effect size in the difference of mean FGF23 level. The minimum required sample size was 92 (46 cases and 46 healthy individuals) [15]. Inclusion criteria were patients on hemodialysis randomly selected from the Dialysis Unit at Aswan University Hospital aged 18 years or older and 48 matched healthy control subjects with normal kidney function (eGFR >60 ml/min/1.73m^2) and of the same age, sex, and body mass index (BMI). On the other hand, patients treated with hemodialysis for <12 months and those with previous Para thyroidectomy, parathyroid ablation, history of solid organ transplantation, and treatment with immunosuppression or chemotherapy in the two years prior to the study were excluded from the study.

2.1. Procedure

All patients were subjected to the following:

1. Full history taking.
2. Thorough clinical examination.
3. Biochemical assessments that including Fasting serum concentrations of creatinine, calcium, phosphate, eGFR. Serum PTH is determined using ELISA kit .Serum FGF23 levels were measured using the FGF23 ELISA kit. and was done by enzyme-linked immunosorbent assay technique.
4. Vascular imaging that includes Lateral lumbar radiography. Lateral lumbar X-rays were performed to assess the presence of abdominal aortic calcification in the same day with blood sampling was draw. Abdominal aortic calcification (AAC) score calculates by one experienced radiologist blinded to group and clinical information by determine the calcified deposits at the anterior or posterior wall in the abdominal aorta at each lumbar vertebral segment (L1–L4) and give score from 0 to 4 using the affected segments score (scale 0–4), in this score the number of individual aortic segments which showed any calcification were calculated.

2.2. Statistical analysis

Results were expressed as means ± standard deviation (SD) or median (interquartile range) for continuous variables and as frequencies and percentage for categorical variables. Chi-square test to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data. Wilcoxon signed a test for comparison between two dependent groups for non-parametric data. Spearman correlations analyzed the correlation between the score of abdominal aortic calcification and the level of FGF-23 serum and with different parameters in the two studied groups. Multivariate logistic regression analysis was performed to investigate the effect of each independent variable simultaneously with aortic calcification. Results were presented as OR (odds ratio). Diagnostic validity test included sensitivity and specificity. Receiver-operating characteristic (ROC) curves assessed the predictive value of FGF23 in the diagnosis of abdominal aortic calcification. The significant result was considered if the $P < 0.05$ considered statistically significant (At 95% level of confidence). All tests were performed using SPSS version 26.0 [16].

2.3. Ethical Consideration

IRB approval was obtained from the Medical Ethic Committee, Faculty of Medicine, Aswan University (IRB no. 332/2/19). The study was carried out in accordance with the Helsinki Declaration guidelines [17] and in line with STROBE checklist for research ethics [18]. The title and objectives of the study were explained to them to ensure their cooperation. A written informed consent was obtained from the patient before the participation in the study. All collected data was confidential and was used for the purpose of scientific research only. Every research participant had the complete right and freedom to withdraw at any time from the study without any consequences on the medical service provided.

3. Results and discussion

This case-control study included 48 patients with end stage renal disease on hemodialysis randomly selected from Dialysis Unit at Aswan University Hospital and 48 matched healthy control subjects. The demographic and clinical characteristics of study participants are presented in table 1. The mean age of the HD patients was 45.2 ± 12.2 years, 23 males (47.9%) and 25 females (54.2%). Hemodialysis treatment mean duration was 83.3 ± 38.9 months. The mean age of the matched healthy controls was 45.3 ± 13.3 years, 22 males (45.8%) and 26 females (52.1%). There were non-significant differences between the two groups as regard age and sex. In addition, compared with controls, cases were more likely to have comorbidities including hypertension, CVD, and hyperlipidemia ($p<0.001$,

0.007 and 0.011, respectively), while diabetes mellitus showed no statistically significant differences. Likewise, patients were more likely to receive calcium supplements, calcitriol, and ACEi/ARB (p<0.001, <0.001 and 0.012, respectively) than controls. As well, the mean BMI for cases was 25.06±4.32 kg/m^2 vs. 25.92±3.80 kg/m^2 for control (p <0.001). Elevated systolic and diastolic blood pressure were found in cases than controls (153.2 ± 16.1 vs. 127.7 ± 20.4 mmHg; p = 0.001) for SBP, while DBP (91.2 ± 9.6 vs. 82.6 ± 12.3 mmHg; p <0.001). Also, elevated brachial pulse pressure in cases than controls (62.1 ± 10.3 vs. 45.3 ± 10.9 mmHg; p <0.001) (Table 1). As shown in table 2, patients had higher mean eGFR was 6.1 ± 2.4 mL/min/1.73m2 than control 84.8 ± 24.9 mL/min/1.73m2) (p =0.004). In addition, HD patients had significantly higher levels of serum levels of creatinine, calcium, and phosphate more in cases than in controls. Further, compared with controls, cases had significantly higher levels of serum levels of PTH and plasma FGF23 compared with i.e., median serum PTH was 306 (82.8-764.9 pg/dl) in cases vs. 32.8 (29.2-39.2 pg/dl) in controls; p <0.001. Likewise, when comparing the two groups, it was found that statistically significant increased median level of FGF23 among cases in comparison to those among control i.e., the median serum FGF23 was 785.4 (458.7-1098.1 pg/dl) in cases vs. 80.27 (56.9 - 98.8 pg/dl) in controls; p 0.032. In the current study, there was statistically positive high significant correlation between serum FGF23 levels and AAC score in both HD (r=0.82, p<0.001) and control (r=0.626, p<0.001). Likewise, there were statistically significant moderate to high positive correlations between FGF23 levels with BMI and PTH levels only in cases (r=0.299, p=0.039 and r=0.703, p<0.001, respectively). Also there was a statistically significant moderate to high positive correlation between FGF23 levels with age, SBP, DBP and PP only in control group (r=0.632, p<0.001; r=0.57, p<0.001; r=0.447, p=0.001; and r=0.626, p<0.001, respectively) and of no statistical significance in the dialysis group (Table 3). Moreover, the presence of aortic calcification was independently associated with higher FGF-23, and it was the only significant explanatory and predictor for AAC (AOR = 1.03; 95% CI, 1.004 to 1.051; p = 0.018) among hemodialysis patients in the multivariable regression analysis model adjusted for (age, BMI, calcium, phosphate and PTH levels) as shown in Table 4. Receiver operator characteristic (ROC) curve analysis was performed and showed that serum FGF-23 as a potential predictor of abdominal aortic calcification (AUC=0.914) in HD patients at the cut-off point of 679 pg/ml with a sensitivity of 100% and a specificity of 86.4% (95% CI 0.849-0.980, p =0.001) (Fig.1). Examples of abdominal aortic calcifications of the studied population (Fig. 2-3).

Vascular calcifications, found in hemodialysis patients represented one of the factors contributing to the extremely high cardiovascular mortality for hemodialysis patients when compared with the general population. Aortic calcification was shown to be associated with coronary calcification [19] and mortality [20] in HD patients. The CKD-MBD Working Group Guidelines recommend the use of non-invasive and inexpensive radiographic examination of vascular calcification, including abdominal aortic calcification, which allows assessment for the presence and semi-quantitative [5]. The main finding of this study was that a single measurement of the plasma FGF-23 level was shown to be a significant predictor of vascular calcification of the abdominal aorta in hemodialysis patients. Elevated circulating FGF23 levels were associated with aortic calcification independent of other BMM markers evaluated in this study compared with controls. Vascular calcification is prevalent in chronic hemodialysis patients. Its prevalence varies significantly from 60% to 100%, depending on the location of the examination and diagnostic method used and the area where the study was conducted [21]. In our study, we used the affected segments score (scale 0–4) with lateral lumber radiography to evaluate AAC in the studied population and we found that the prevalence of AAC was 54.2% among HD subjects with a significantly higher AAC score in the study (p<0.001). These results were supported by a cross-sectional study conducted by Elsamman et al reported that the prevalence of VC in patients with HD was 50% through examination by plain X-ray pelvis and hands [22]. In addition, in our study it was found that patients had significant higher brachial PP, eGFR and serum creatinine, phosphate, PTH and FGF23 levels than in controls when we compared the study population who had aortic calcification while cases with calcification had a significant higher BMI, serum levels of PTH and FGF23 than HD patients without any calcifications. Moreover, in the current study, serum FGF-23 was significantly higher in HD group than in CKD and control groups (p = 0.032). These results were supported by the study conducted by Viaene et al. on the residual renal function and reported a strong and independent relationship with serum phosphorus and FGF-23 levels in dialysis patients [23]. Also Dewang Zeng et al. found that the mean FGF23 level in CKD-MBD patients was significantly higher than that in healthy controls [24]. Additionally, in this study, there was a statistically positive significant correlation between serum FGF23 levels with AAC score in cases. Also, there were statistically significant positive correlations between serum FGF23 levels with BMI and serum PTH levels in HD group and of no statistical significance in the control group. Also, there was a statistically positive significant correlation between AAC score with age, BMI and serum PTH levels in HD group and of no statistical significance in the control group. The present study affirmed the strong correlation between AAC and age. In a comprehensive systemic review of 30 studies over 20 years, it was found that age was one of the fundamental correlates with VCs in patients with ESRD [25]. In the multivariable regression analysis, presence of aortic calcification was independently associated with higher FGF-23, and it was the only significant explanatory and predictor variable for AAC among hemodialysis patients in the multivariable regression analysis adjusted for age, BMI, calcium, phosphate and PTH levels. These results were in agreement with results reported by Desjardins et al. who demonstrated that plasma FGF23 levels were independently correlated with aortic calcification scores in 142 patients with a wider spectrum of renal dysfunction (CKD 2–5) inclusive of patients on maintenance dialysis [9]. Another study performed on 30 CKD and 30 HD patients reported that there were statistically significant positive correlations between FGF-23, and both left ventricular mass index and VC [26].

Table 1. Baseline Characteristics of the studied Cohort

Variable	Hemodialysis Case (n=48)	Controls (n=48)	P value
Age (year)			
Mean ± SD	45.21±12.17	45.33±13.33	0.997*
Median (interquartile range)	44 (35-57.5)	50 (33.25-58)	
Minimum–maximum	25-64	20-60	
Gender			
Females	25 (54.2%)	26 (52.1%)	0.838**
Males	23 (47.9%)	22 (45.8%)	
Hemodialysis duration (month)			
Mean ± SD	83.29±38.89		
Median (interquartile range)	84 (48-117)	--	
Minimum–maximum	12-156		
Body mass index (kg/m^2)			
Mean ± SD	25.06±4.32	25.92±3.80	**<0.001***
Median (interquartile range)	24.3 (21.65-28.875)	26.1 (23.425-28.475)	
Minimum–maximum	18-34.6	16.5-35.4	
Diabetes mellitus			
No	44 (91.7%)	43 (89.6%)	0.726**
Yes	4(8.3%)	5 (10.4%)	
Hypertension			
No	6 (12.5%)	33 (68.8%)	**<0.001****
Yes	42 (87.5%)	15 (31.3%)	
Cardiovascular diseases			
No	32 (66.7%)	43 (89.6%)	**0.007****
Yes	16 (33.3%)	5 (10.4%)	
Hyperlipidemia			
No	30 (62.5%)	41 (85.4%)	**0.011****
Yes	18 (37.5%)	7 (14.6%)	
Systolic blood pressure (mmHg)			
Mean ± SD	153.23±16.12	127.71±20.44	**0.001***
Median (interquartile range)	160 (140-160)	120 (112.5-140)	
Minimum–maximum	90-180	90-180	
Diastolic blood pressure (mmHg)			
Mean ± SD	91.15±9.63	82.60±12.33	**<0.001***
Median (interquartile range)	90 (86.25-100)	82.5 (72.5-90)	
Minimum–maximum	60-110	60-100	
Pulse pressure			
Mean ± SD	62.08±10.25	45.29±10.92	**<0.001***
Median (interquartile range)	60 (60-70)	40 (40-50)	
Minimum–maximum	30-80	30-80	
Medication use			
Calcitriol			
No	23 (47.9%)	48 (100%)	**<0.001*****
Yes	25 (52.1%)	0 (0.0%)	
Calcium Supplements			
No	17 (35.4%)	48 (100%)	**<0.001*****
Yes	31 (64.6%)	0 (0.0%)	
Cinacalcet			
No	45 (93.8%)	48 (100%)	0.078***
Yes	3 (6.3%)	0 (0.0%)	
ACEi/ARB			
No	33 (68.8%)	43 (89.6%)	**0.012*****
Yes	15 (31.3%)	5 (10.4%)	

*Independent Sample t-test was used to compare the differences in Mean between groups
**Chi-square test was used to compare the frequency differences between groups
***Fisher's exact test was used to compare the frequency differences between groups

Table 2. Laboratory investigations of the studied population

Variable	Hemodialysis Cases (n=48)	Controls (n=48)	P value
Creatinine Mean ± SD Median (interquartile range) Minimum–maximum	 9.7 ± 3.1 9.7 (7.6 - 11.7) 4.2 - 16.3	 0.99 ± 0.3 1 (0.8 - 1.2) 0.3 - 1.5	**<0.001***
eGFR (mL/min/1.73 m^2) Mean ± SD Median (interquartile range) Minimum–maximum	 6.1 ± 2.4 5 (4 - 8) 3 - 13	 84.8 ± 24.9 86 (63.3 - 103) 41 - 148	**0.004***
Calcium (mg/dL) Mean ± SD Median (interquartile range) Minimum–maximum	 9.7 ± 1.4 9.9 (9 - 10.7) 4.4 - 11.5	 9.2 ± 0.7 9.2 (8.9 - 9.9) 7.2 - 10.5	**<0.001***
Phosphate (mg/dL) Mean ± SD Median (interquartile range) Minimum–maximum	 5.6 ± 2.3 5.25 (4 - 6.9) 2.5 - 12.3	 3.6 ± 0.5 3.75 (3.1 - 4) 2.7 - 4.5	**<0.001***
PTH (pg/dl) Median (interquartile range) Minimum–maximum	 306.5 (82.8 - 764.9) 9 - 2436.9	 32.8 (29.1 - 39.2) 22.1 - 45	**<0.001****
FGF-23 (pg/ml) Median (interquartile range) Minimum–maximum	 785.4 (458.7 - 1098.1) 283.3 - 1360	 80.3 (56.9 - 98.8) 30.1 - 127.9	**0.032****

*Independent Sample t-test was used to compare the differences in Mean between groups
*Mann Whitney U-test was used to compare the differences in Median between groups

Table 3. Correlation between abdominal aortic calcification score and different parameters in the two studied groups

Parameters	FGF23			
	Hemodialysis patients (n=48)		Controls (n=48)	
	r_s	P-value	r_s	P-value
Age	0.194	0.186	0.632	**< 0.001**
BMI	0.299	**0.039**	0.263	0.071
SBP	-0.153	0.298	0.57	**< 0.001**
DBP	-0.215	0.142	0.447	**0.001**
Creatinine	0.155	0.294	0.206	0.16
Ca	-0.079	0.592	-0.144	0.33
PO4	0.07	0.637	-0.145	0.325
PTH	0.703	**< 0.001**	0.129	0.383
AAC score	0.82	**< 0.001**	0.626	**< 0.001**
PP	0.014	0.924	0.626	**< 0.001**

Table 4. Multivariable logistic regression analysis of factors associated with the presence of AAC in hemodialysis patients.

Variable	Odds ratio (95% confidence interval)	P value
Age	0.983 (0.851 - 1.134)	0.814
BMI	0.907 (0.642 - 1.280)	0.579
Calcium	0.975 (0.308 - 3.084)	0.965
Phosphate	0.502 (0.218 - 1.157)	0.106
PTH	0.995 (0.989 - 1.00)	0.061
FGF23	1.027 (1.004 - 1.051)	**0.018**

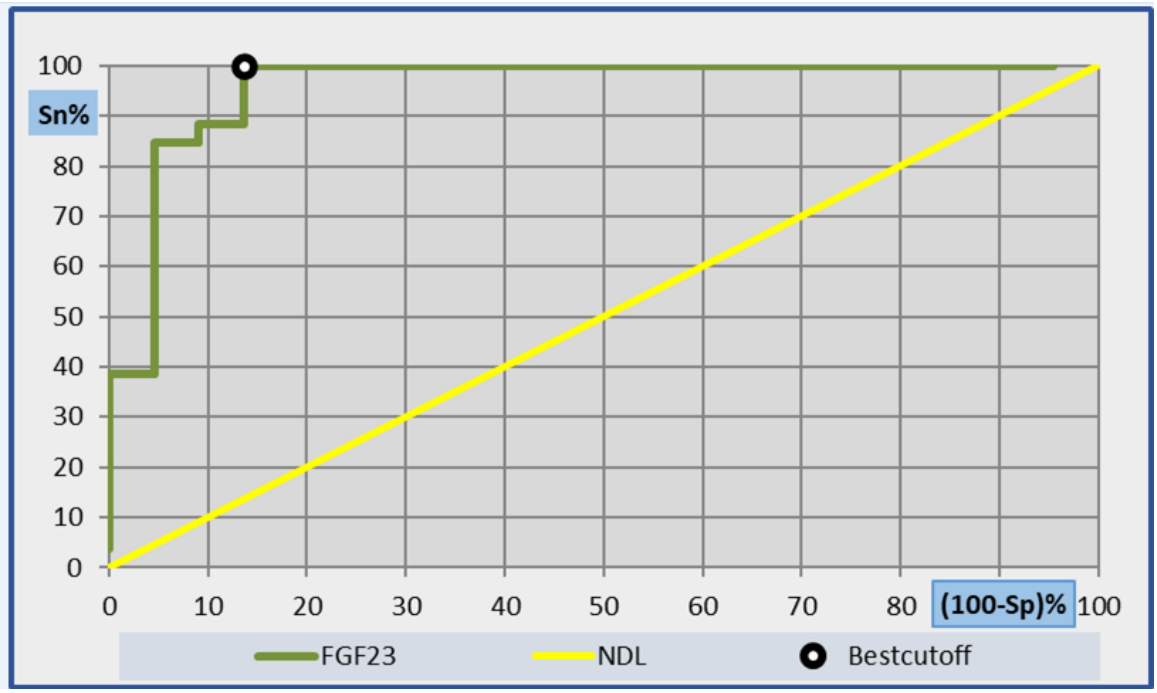

Figure 1. ROC curve analysis showing serum FGF-23 as a potential predictor of abdominal aortic vascular calcification.

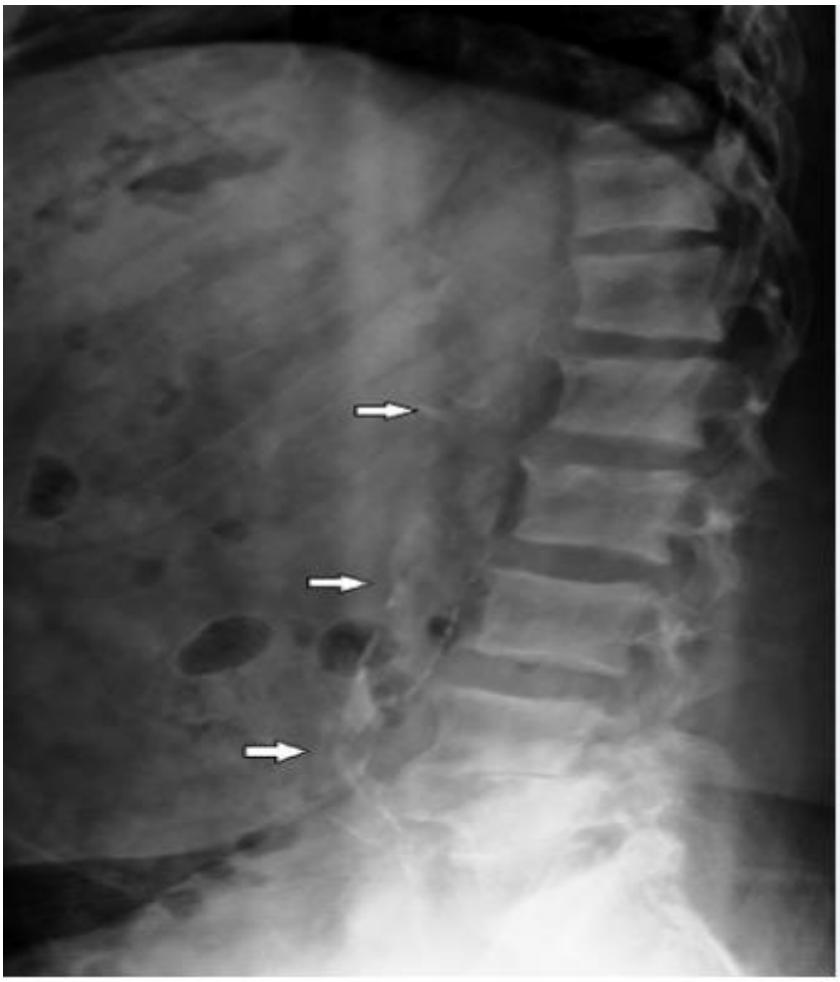

Figure 2. Lateral abdominal radiographic view of a 34-year-old male receiving hemodialysis showing severe aortic calcifications (both posterior and anterior) in front of L1 to L4 vertebrae with affected segments score for aortic calcification = 4.

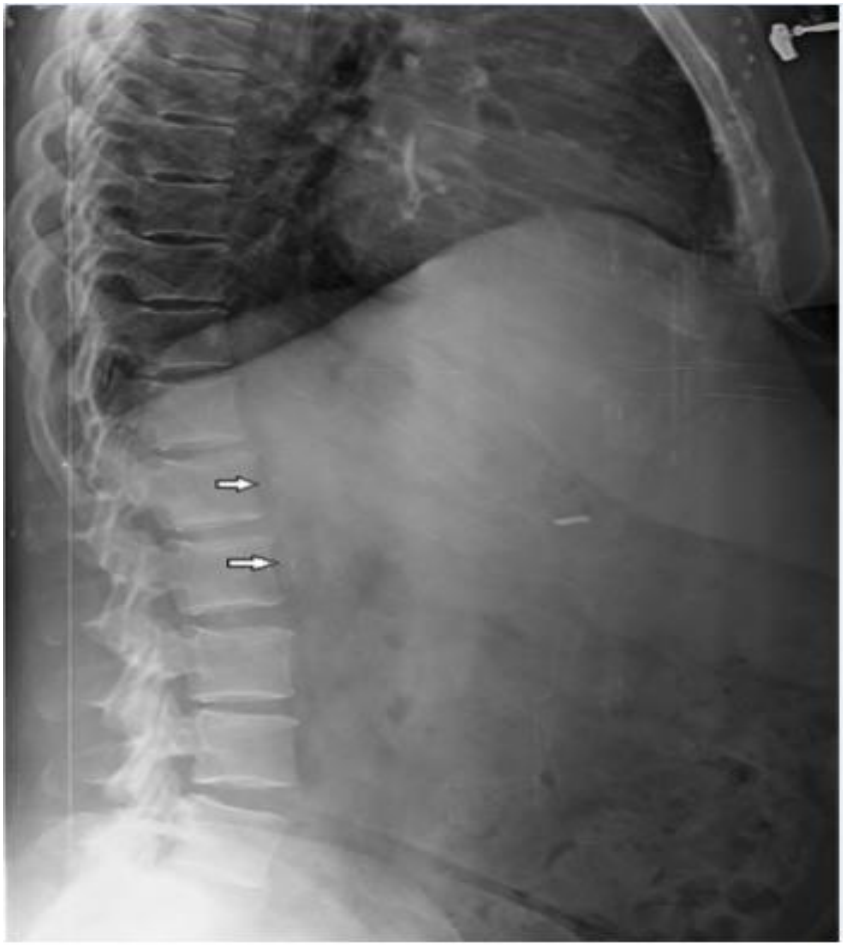

Figure 3. Lateral abdominal radiographic view of a 55-year-old woman from control group demonstrating aortic calcification. Affected segments score for aortic calcification.

In this study, ROC curve analysis showed that the value of FGF23 in the diagnosis of abdominal aortic calcification was higher than previous studies (AUC=0.914) in HD patients, suggesting that serum FGF-23 was a potential predictor of abdominal aortic calcification and were a high-risk population of cardiovascular diseases as found by Zhang et al. who demonstrated that FGF 23 predicts coronary calcification and poor prognosis in patients with CKD [27]. Another study confirmed that the serum FGF23 concentrations are useful for clinical prediction of abdominal aortic calcification, and our study was consistent with it [28]. The cutoff point, sensitivity and specificity were higher than previous studies that reported by Muzasti et al. who found that FGF-23 level for the prediction of AAC in HD patients was 277 pg/mL with the 94% sensitivity and 84% specificity [29]. While Ibrahim et al. reported that, the cut-off points for FGF-23 to predict breast arterial calcification (BAC) in the women patients with CKD was 77.5 ng/ml and with the 78% sensitivity and the 76% specificity [30].

3.1. Strengths and Limitations

The study harbor some limitations; single radiologist performed assessment; progression of AAC was not assessed as follow-up lumbar X-ray was not obtained; the need to be correlated with Klotho as it is an essential co-factor for FGF23 and with other markers of chronic inflammation in hemodialysis like IL-6; comparing these results to patients with peritoneal dialysis; several co-existing conditions, such as underlying diabetes, CVD and physical inactivity, that were prevalent in the HD group may have confounded the observed associations in this study; information on dietary phosphate intake and urinary phosphate excretion, which may directly influence change in FGF23, was not collected in this study and evaluation of cardiac function and structure was also not collected in this study and may have provided valuable information on the link between FGF23 and cardiovascular disease. Despite limitations, this study is the first one which vascular calcification in hemodialysis patients in Aswan Governorate, and one of few studies about vascular calcification in Egypt. In our study, a high prevalence of aortic calcification in hemodialysis patients is detectable using lateral lumbar radiography of the abdominal aorta.

Presence of aortic calcification was independently associated with higher serum FGF23 level independent of other BMM markers evaluated in this study in both CKD and controls. Serum FGF23 level may be proposed as a promising diagnostic marker for abdominal aortic calcification in hemodialysis patients. Which may have an impact on mortality among HD patients. Lateral lumbar radiography scan can be used to evaluate aortic wall calcification. It is simple, inexpensive, and useful for an initial diagnosis of VC among HD patients, which may be enough to detect higher risk.

4. Conclusion

In conclusion, it was found that a high prevalence of vascular calcifications of abdominal aorta in hemodialysis patients as patients diagnosed to have vascular calcifications. Also, HD patients had significantly higher brachial PP, eGFR and serum creatinine, phosphate, PTH and FGF23 levels than in controls when we compared the study population who had aortic calcification (i.e. AAC ≥ 1). While the HD patients with calcification had a significant higher BMI, serum levels of PTH and FGF23 than HD patients without any calcifications. As well, there was a statistically positive significant correlation between serum FGF23 levels with AAC score in HD patients. Also there were statistically significant positive correlations between serum FGF23 levels with BMI and serum PTH levels in HD group. Whereas there was a statistically positive significant correlation between AAC score with age, BMI and serum PTH levels in HD group. In the multivariable regression analysis, presence of aortic calcification was independently associated with higher FGF-23, and it was the only significant explanatory and predictor variable for AAC) among hemodialysis patients in the multivariable regression analysis adjusted other confounders.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

None.

Author Contributions

Raghda G. Mostafa (RGM); concept, design, literature search, clinical studies, statistical analysis, manuscript preparation, editing and review Mohamed G. Saadi (MGS); design, literature search, manuscript preparation and review. Hala A. Mahmoud (HAM); clinical and laboratory work. Ahmed H. Ahmed (AHA): radiological study, literature search, clinical studies, manuscript editing.

References

[1] S. Thompson, M. James, N. Wiebe, B. Hemmelgarn, B. Manns, S. Klarenbach, M. Tonelli. (2015). Cause of death in patients with reduced kidney function. Journal of the American Society of Nephrology: JASN. 26 (10), 2504.

[2] D. Russo, S. Corrao, Y. Battaglia, M. Andreucci, A. Caiazza, A. Carlomagno, B. Scognamiglio. (2011). Progression of coronary artery calcification and cardiac events in patients with chronic renal disease not receiving dialysis. Kidney international. 80 (1), 112-118.

[3] M. Briet, K.D. Burns. (2012). Chronic kidney disease and vascular remodelling: molecular mechanisms and clinical implications. Clinical science. 123 (7) 399-416.

[4] C.M. Rhee, C.P. Kovesdy. (2015). Spotlight on CKD deaths—increasing mortality worldwide. Nature Reviews Nephrology. 11 (4), 199-200.

[5] T. Isakova, T.L. Nickolas, M. Denburg, S. Yarlagadda, D.E. Weiner, O.M. Gutiérrez, H. Kramer. (2017). KDOQI US commentary on the 2017 KDIGO clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). American Journal of Kidney Diseases. 70 (6) 737-751.

[6] K. Nitta. (2011). Vascular calcification in patients with chronic kidney disease. Therapeutic Apheresis and Dialysis. 15 (6) 513-521.

[7] R. Jimbo, F. Kawakami-Mori, S. Mu, D. Hirohama, B. Majtan, Y. Shimizu, T. Shimosawa. (2014). Fibroblast growth factor 23 accelerates phosphate-induced vascular calcification in the absence of Klotho deficiency. Kidney international. 85 (5) 1103-1111.

[8] D. Zhu, N.C. Mackenzie, J.L. Millan, C. Farquharson, V.E. MacRae. (2013). A protective role for FGF-23 in local defence against disrupted arterial wall integrity?. Molecular and cellular endocrinology. 372 (1-2) 1-11.

[9] L. Desjardins, S. Liabeuf, C. Renard, A. Lenglet, H.D. Lemke, G. Choukroun, European Uremic Toxin (EUTox) Work Group. (2012). FGF23 is independently associated with vascular calcification but not bone mineral density in patients at various CKD stages. Osteoporosis International. 23 2017-2025.

[10] M.M. Nasrallah, A.R. El-Shehaby, M.M. Salem, N.A. Osman, E. El Sheikh, U.A. Sharaf El Din. (2010). Fibroblast growth factor-23 (FGF-23) is independently correlated to aortic calcification in haemodialysis patients. Nephrology Dialysis Transplantation. 25 (8) 2679-2685.

[11] S, Chande, C. Bergwitz. (2018). Role of phosphate sensing in bone and mineral metabolism. Nature Reviews Endocrinology. 14 (11) 637-655.

[12] L. Nguyen-Yamamoto, A.C. Karaplis, R. St–Arnaud, D. Goltzman. (2017). Fibroblast growth factor 23 regulation by systemic and local osteoblast-synthesized 1, 25-dihydroxyvitamin D. Journal of the American Society of Nephrology: JASN. 28 (2) 586.

[13] I. Urakawa, Y. Yamazaki, T. Shimada, K. Iijima, H. Hasegawa, K. Okawa, K., T. Yamashita. (2006). Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature. 444 (7120) 770-774.

[14] O.M. Gutiérrez, J.L. Januzzi, T. Isakova, K. Laliberte, K. Smith, G. Collerone, M. Wolf. (2009). Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. Circulation. 119 (19) 2545-2552.

[15] A.G. Dean, T.G. Arner, G.G. Sunki, R. Friedman, M. Lantinga, S. Sangam, R.F. Fagan. (2011). Epi Info™, a database and statistics program for public health professionals. CDC, Atlanta, GA, USA. 1.

[16] K.D.V. Prasad, R. Vaidya, V.A. Kumar. (2016). Teacher's performance as a function of occupational stress and coping with reference to CBSE affiliated school teachers in and around Hyderabad: a multinomial regression approach. Psychology. 7 (13) 1700-1718.

[17] World Medical Association (2013). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 310 (20) 2191-4.

[18] V. Gallo, M. Egger, V. McCormack, P.B. Farmer, J.P. Ioannidis, M. Kirsch-Volders, P. Vineis. (2011). in Epidemiology-Molecular Epidemiology (STROBE-ME): an extension of the STROBE statement. Eur J Epidemiol. 26 797-810.

[19] R.N. Foley, D.T. Gilbertson, T. Murray, A.J. Collins. (2011). Long interdialytic interval and mortality among patients receiving hemodialysis. New England Journal of Medicine. 365 (12) 1099-1107.

[20] K. Yamada, S. Fujimoto, T. Tokura, K. Fukudome, H. Ochiai, H. Komatsu, T. Eto. (2005). Effect of sevelamer on dyslipidemia and chronic inflammation in maintenance hemodialysis patients. Renal failure. 27 (4) 361-365.

[21] G. Rosa-Diez, G. Bratti, G. Filannino, A. Peñalba, F. Otreras, M. Ledesma, H. Trimarchi. (2017). Prevalence of factors related to vascular calcification in patients with chronic kidney disease on dialysis. Medicina (Buenos Aires). 77 (3) 207-213.

[22] Elsamman, Mahmoud Kamal, Mohamed Abdel Wahab Ezzat, Medhat Ibraheem Mohammad, Raghda Gamal Mostafa, and Ali Taha Ali Hassan. 2017. 'Assessment of Arterial Stiffening and Vascular Calcifications in End-Stage Renal Disease Patients', World Journal of Cardiovascular Diseases, 7: 131-43.

[23] L. Viaene, B. Bammens, B.K. Meijers, Y. Vanrenterghem, D. Vanderschueren, P. Evenepoel. (2012). Residual renal function is an independent determinant of serum FGF-23 levels in dialysis patients. Nephrology Dialysis Transplantation. 27 (5) 2017-2022.

[24] D. Zeng, A. Zha, Y. Lei, Z. Yu, R. Cao, L. Li, S. Luan. (2023). Correlation of Serum FGF23 and Chronic Kidney Disease-Mineral and Bone Abnormality Markers With Cardiac Structure Changes in Maintenance Hemodialysis Patients. Evidence-Based Complementary and Alternative Medicine, 2023.

[25] P.A. McCullough, K.R. Sandberg, F. Dumler, J.E. Yanez. (2004). Determinants of coronary vascular calcification in patients with chronic kidney disease and end-stage renal disease: a systematic review. Journal of nephrology. 17 (2) 205-215.

[26] S.A. Zaki, I.E. El Gohary, E.M. Elsharkawy, D.I. Hashad, D.M. Emara, M.R. El Hameed. (2018). Fibroblast growth factor-23 and vascular calcification in chronic kidney disease and hemodialysis patients. Journal of The Egyptian Society of Nephrology and Transplantation. 18 (1) 17.

[27] M. Zhang, J. Yan, M. Zhu, Z. Ni. (2015). Fibroblast growth factor 23 predicts coronary calcification and poor prognosis in patients with chronic kidney disease stages 3-5D. Annals of Clinical & Laboratory Science. 45 (1) 17-22.

[28] T. Ohtake, S. Kobayashi. (2017). Impact of vascular calcification on cardiovascular mortality in hemodialysis patients: clinical significance, mechanisms and possible strategies for treatment. Renal Replacement Therapy. 3 (1) 1-11.

[29] R.A. Muzasti, N.D. Lubis. (2021). Diagnostic value of fibroblast growth factor 23 for abdominal aortic calcification in Indonesian hemodialysis patients. Tzu-Chi Medical Journal. 33 (2) 154.

[30] B.O. Ibrahim, G.A. Tawfik, H. Ahmed, H.H. Omar. (2022). Association of Fibroblast Growth Factor-23 and Early Detection of Breast Arterial Calcification in Different Stages of Chronic Kidney Disease Patients. Suez Canal University Medical Journal. 25 (1) 80-91.