Original Article

The Change of Serum FGF-23 Levels Predicts the Progression of Renal Function in Chronic Kidney Disease Patients

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Background: The role of elevated baseline fibroblast growth factor 23 (FGF-23) levels on the progression of renal function in long term (years) follow-up studies is not yet established.

Objective: To circumvent the confounding factors occurring during the study duration, the authors examined the roles of the changing values of FGF-23 and other risk factors on progression of renal function after a shorter term (months) follow-up.

Materials and Methods: The present study was a 12-week prospective cohort study to determine the association between traditional and non-traditional risk factors on the progression of renal function.

Results: Sixty-five chronic kidney disease (CKD) patients were included. After a 12-week follow-up, significant increases of serum creatinine, cystatin C, vitamin D level, and FGF-23 levels were observed. The delta FGF-23 values increased progressively according to the staging of the CKD. The baseline parathyroid hormone level, which was in the recommended range following the KDIGO guideline, and the delta FGF-23 values were the significant parameters that had association with the decline of the estimated glomerular filtration. There was a positive association between delta FGF-23 and delta 25-OH vitamin D values.

Conclusion: The increasing change in serum FGF-23 level is significantly correlated with declining renal function. Thus, delta FGF-23 value could be utilized as a suitable biomarker for following and detecting CKD progression.

Keywords: FGF-23, Vitamin D, CKD progression, Biomarker

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Fibroblast growth factor 23 (FGF-23), a hormone mainly excreted from the osteocytes, increases urinary phosphate excretion, decreases active vitamin D synthesis, and inhibits parathyroid hormone (PTH) synthesis and secretion. Meanwhile, FGF-23 is stimulated by high phosphorus intake, hyperphosphatemia, active vitamin D, and PTH[1]. Besides mineral metabolism, FGF-23 directly activates the renin-angiotensin-aldosterone system (RAAS)[2]. FGF-23 concentrations rise early in chronic kidney disease (CKD) before the elevation in PTH and the onset of apparent hyperphosphatemia[3]. A significant inverse correlation was observed between FGF-23 levels and estimated glomerular filtration rate (eGFR)[4,5]. Despite that the increase in FGF-23 is recognized to be a proper physiological response to maintain normal phosphorus homeostasis, the consistently heightened FGF-23 levels eventually result in increasing mortality and cardiovascular events in CKD patients[6].

Several previous studies have attempted to examine the association between the baseline levels of FGF-23 and consequent renal function[4,7]. Although many reports have demonstrated the relationship between the increased baseline levels of FGF-23 levels and the decline in renal function as well as

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elevation in incidences of CKD and end stage renal disease (ESRD)[5,7-9], a considerable number of studies could not show such interrelation, especially after adjusted analysis[10,11]. The follow-up duration between the measurements of the baseline FGF-23 levels and renal function in these studies ranged from 2 to 5.5 years[12]. The discrepancies of the results might be caused by the differences in both traditional and non-traditional risk factors for progression of renal function including blood pressure, proteinuria, oxidative stress markers, and CKD-mineral bone disease (CKD-MBD) parameters that dissimilarly occur in CKD patients during a long-term follow-up period. In this regard, the changing values of all the above parameters including FGF-23 within a shorter duration (months) might delineate the precise role of these parameters on consequent renal function. Of more importance, CKD patients with consequently declined renal function would promptly undergo investigations regarding the causes of deteriorated renal function and instantly receive appropriate modalities of treatment.

The present prospective cohort study was conducted in the CKD patients to determine the association between the baseline as well as the changing values of the traditional and the non-traditional risk factors for progression of renal function and the changes in renal function following a 3-month follow-up.

Materials and Methods

Study design

The present study was a prospective cohort study conducted at the outpatient clinic King Chulalongkorn Memorial Hospital, Bangkok, Thailand. Thai CKD patients were screened between July 2014 and February 2015. The primary end point of the study was the correlation between the risk factors of CKD and the change of renal function.

Study population

The inclusion criteria comprised patients who were 18 years or older with eGFR of 15 to 60 mL/minute/1.73 m² (CKD stage 3 to 4). The eGFR was calculated with serum creatinine concentrations by using Thai-Modification of Diet in Renal Disease (MDRD) formula. Patients having active glomerulonephritis, receiving immunosuppressive drugs within three months before enrollment or having been adjusted the doses of RAAS blockades such as angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers (ACEIs/ARBs) within three months before enrollment were excluded.

Data collection

All patients underwent blood pressure measurement and blood samples were obtained at baseline and at the twelfth week of follow-up. The laboratory parameters including serum creatinine, cystatin C, urine protein to creatinine ratio (UPCR, g/g), high sensitive C-reactive protein (hs-CRP), serum calcium, phosphate, albumin, intact PTH, and FGF-23 levels were determined. The intact PTH levels were measured using a chemiluminescence immunoassay on a Roche Elecsys 2010 Analyzer, this assay detected both intact PTH and a fragment containing amino acids 7 to 84, the reference range is 15.0 to 65.0 pg/mL. The FGF-23 levels were assessed using a Human intact FGF-23 ELISA kit (Millipore Corporation, Billerica, MA, United States). The lowest limit of detection was 3.5 pg/mL with an Intra-assay and inter-assay coefficient of variations (CVs) of less than 10%.

Statistical analysis

The authors calculated and found a sample size of 65 patients was needed for 80% power to detect an expected correlation coefficient for FGF-23 levels and changes of eGFR 0.35 with two-sided significance level of 0.05.

Baseline characteristics were presented in mean ± standard deviation (SD) or percentage. Categorical data were reported in numbers and percentages while continuous variables were presented in mean ± SD. Univariate and multivariate linear regression analyses were performed to assess the association of risk factors and CKD progression. Data were analyzed using the IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Of the total 68 eligible CKD patients, three patients were excluded due to inadequate blood samples. The mean age was 63.02±12.33 years old, and 47.7% were male. Diabetic kidney disease was the most common cause of CKD (52.3%). Fifty-four percent of the patients received ACEIs or ARBs. All patients obtained nutritional vitamin D due to vitamin D deficiency and 48% received active vitamin D. The laboratory values at baseline and at the 12-week follow-up are illustrated in Table 1. At the 12-week follow-up, a significant increase of serum creatinine, cystatin C, vitamin D level, and FGF-23 levels was observed, while there was a significantly decreased

Table 1. Baseline and follow clinical and laboratory parameters

Characteristics (n=65)	Baseline Mean±SD	At 12th week Mean±SD	p-value
Serum creatinine (mg/dL)	2.29±0.84	2.44±1.08	0.005*
eGFR (mL/minute/1.73 m^2)	38.32±11.23	37.87±13.39	0.547
Serum cystatin C (mg/L)	2.12±0.63	2.17±0.67	0.043*
Serum calcium (mg/dL)	9.45±0.47	9.25±0.57	0.116
Serum phosphate (mg/dL)	3.63±0.61	3.80±0.62	0.092
Serum PTH (pg/mL)	85.27±51.67	78.57±58.45	0.115
Serum 25-hydroxy vitamin D (ng/mL)	17.57±6.24	32.02±11.79	<0.001*
Serum FGF-23 (pg/mL)	9.95±7.29	13.06±10.14	<0.001*
Serum albumin (g/dL)	3.91±0.37	3.29±0.34	0.564
UPCR (g/g)	3.60±3.40	2.39±2.08	0.001*
Serum hs-CRP (mg/L)	2.97±4.10	3.85±5.51	0.072
Systolic blood pressure (mmHg)	137.42±15.84	136.57±18.13	0.820
Diastolic blood pressure (mmHg)	76.64±11.08	78.12±11.44	0.318

eGFR=estimated glomerular filtration rate; PTH=parathyroid hormone; FGF-23=fibroblast growth factor-23; UPCR=urine protein to creatinine ratio; hs-CRP=high sensitive C-reactive protein; SD=standard deviation

* p<0.05 is statistical significance

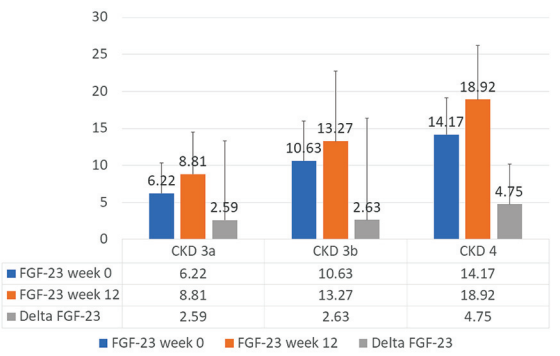

Figure 1. The baseline and 12-week follow-up of serum FGF-23 stratified by CKD stage.

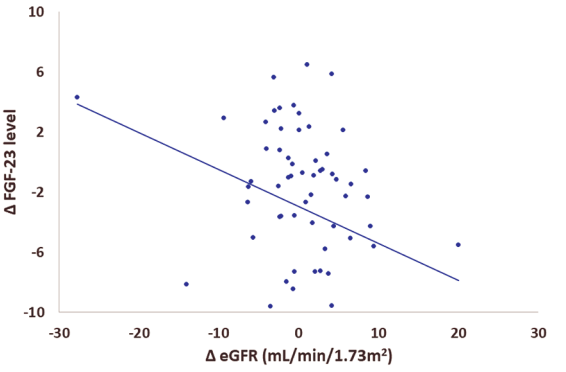

Figure 2. The relationship of Δ serum FGF-23 level and Δ change of eGFR (n=65, r=–0.25, R^2=0.07, p=0.039).

UPCR (Table 1).

As depicted in Figure 1, the levels of FGF-23 at baseline and at 12-week follow-up progressively increased according to the more advance in stages of CKD. Of interest, the delta FGF-23 values also exhibited the similar pattern of progressive increase following the progressive stages of CKD.

The authors further examined the role of delta FGF-23 values and renal function. As illustrated in Figure 2, there was a significant inverse correlation between delta changed of FGF-23 with delta changed of eGFR in the unadjusted model (r=–0.25, R^2=0.07, p=0.039). By using univariate and multivariate adjusted models, the authors further explored the association between the baseline values and the delta change of values on the delta change of eGFR (Table 2, 3, respectively). The present study demonstrated a significant association between the baseline intact PTH and the eGFR declination at the twelfth week (p=0.02). However, there were no significant associations between the baseline phosphate levels, FGF-23, hs-CRP, 25-OH vitamin D level, UPCR, or systolic blood pressure and the decline of GFR (Table 2). The increase of serum FGF-23 was the only variable significantly associated with the decrease of eGFR in both univariate and multivariate models. Meanwhile, the delta change of other parameters did not show any significant

Table 2. Univariate and multivariate linear regression analysis of baseline parameters and delta eGFR

Parameter	Delta eGFR (mL/minute/1.73m^2)			
	Univariate analysis		Multivariate analysis	
	Coefficient (95% CI)	p–value	Coefficient (95% CI)	p-value
Baseline phosphate (mg/dL)	–1.004 (–3.13 to 1.12)	0.34	–0.10 (–2.41 to 2.21)	0.93
Baseline PTH (pg/mL)	–0.31 (–0.59 to 0.04)	0.02	–0.35 (–0.06 to –0.01)	0.02
Baseline 25-OH vitamin D level (ng/mL)	0.12 (–0.22 to 0.25)	0.91	-	-
Baseline hs-CRP (mg/L)	–0.19 (–0.55 to 0.16)	0.29	–0.28 (–0.64 to 0.77)	0.12
Baseline FGF-23 (pg/mL)	–0.03 (–0.24 to 0.17)	0.76	-	-
Baseline UPCR (g/g)	–0.71 (–0.51 to 0.366)	0.29	–0.11 (–0.55 to 0.33)	0.62
Baseline systolic blood pressure (mmHg)	0.04 (–0.06 to 0.14)	0.38	0.03 (–0.06 to 0.13)	0.50

eGFR=estimated glomerular filtration rate; PTH=parathyroid hormone; 25-OH vitamin D=25 hydroxy-vitamin D; FGF-23=fibroblast growth factor-23; UPCR=urine protein to creatinine ratio; hs-CRP=high sensitive c-reactive protein; CI=confidence interval

Table 3. Univariate and multivariate linear regression analysis of delta change of parameters and delta eGFR

Parameter	Delta eGFR (mL/minute/1.73m^2)			
	Univariate analysis		Multivariate analysis	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Delta phosphate (mg/dL)	–0.85 (–3.32 to 1.61)	0.49	–1.01 (–3.69 to 1.49)	0.40
Delta PTH (pg/mL)	–0.14 (–0.06 to 0.03)	0.52	–0.02 (–0.06 to 0.02)	0.25
Delta 25-OH vitamin D level (ng/mL)	–0.04 (–0.19 to 0.10)	0.55	-	-
Delta hs-CRP (mg/L)	–0.24 (–0.62 to 0.13)	0.20	–0.31 (–0.71 to 0.08)	0.11
Delta FGF-23 (pg/mL)	–0.25 (–0.48 to –0.01)	0.04	–0.26 (–0.51 to –0.01)	0.04
Delta UPCR (g/g)	0.09 (–0.43 to 0.62)	0.72	-	-
Delta systolic blood pressure (mmHg)	–0.01 (–0.09 to 0.07)	0.81	-	-

eGFR=estimated glomerular filtration rate; PTH=parathyroid hormone; 25-OH vitamin D=25 hydroxy-vitamin D; FGF-23=fibroblast growth factor-23; UPCR=urine protein to creatinine ratio; hs-CRP=high sensitive C-reactive protein; CI=confidence interval

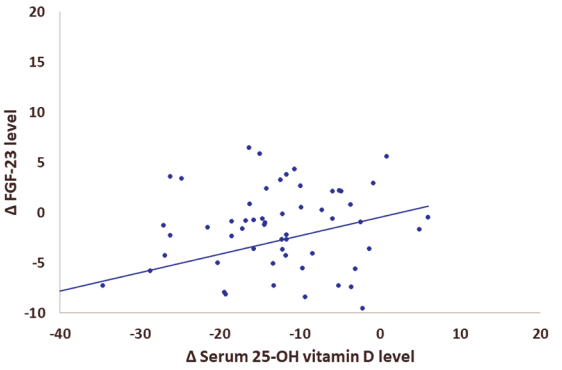

Figure 3. The relationship of Δ FGF-23 level and Δ serum 25-hydroxy vitamin D level (n=65, r=0.18, R^2=0.09, p=0.017).

associations with the delta change of eGFR (Table 3).

As stated earlier, FGF-23 synthesis is stimulated by vitamin D. As shown in Figure 3, a significant positive correlation was seen between the delta change of 25-OH vitamin D and the delta change of FGF-23 level (r=0.18, R^2=0.09, p=0.017).

Discussion

In pre-dialysis CKD patients, the results of the present study have demonstrated significant increases in the levels of serum creatinine, cystatin C, 25-OH vitamin D, and FGF-23 after a 12-week follow-up (Table 1). Although the decrease of eGFR after 12-week follow-up was not statistically significant, it trended to inversely change in the same way with increase of serum creatinine. These might be explained that the eGFR was a more sensitive parameter than serum creatinine and caused the higher standard deviation in limited sample size data.

The delta change of FGF-23 values progressively increased according to the more advance in staging of CKD (Figure 1) and was inversely correlated with the delta change of eGFR (Figure 2). The baseline PTH

level was the only parameter that had association with the decline of eGFR at the twelfth week (Table 2). Among the delta change of values, between the levels at baseline and the 12-week follow-up of the renal progression-associated parameters, the delta change of FGF-23 value was the only variable that was significantly correlated with the decline of eGFR (Table 3). There was a positive association between the delta FGF-23 and delta 25-OH vitamin D values (Figure 3).

A line of evidence has shown that CKD patients are at much higher risk for developing cardiovascular disease (CVD) when compared with the general population. The incidences of congestive heart failure, hospitalization, and mortality are progressively increased following the severity of CKD staging[13,14]. Therefore, retarding or stopping progression of renal function is the goal in management of CKD patients. Indeed, CVD and progression of renal function are driven not only by traditional risk factors, including hypertension, dyslipidemia, diabetes mellitus, and smoking, but also by non-traditional factors, such as uremic toxin accumulation, proteinuria, increased inflammation, elevated oxidative stress, and CKD-MBD related parameters, which consist of serum phosphate, PTH, 25-OH vitamin D, and FGF-23[15-18]. Most previous cohort studies determined the association between the baseline levels of these renal progression-associated factors and renal function after quite a long-term follow-up (years)[5,7,12,19-22]. As such, there could be various confounding effects from the changes in other risk factors differently occurring in the studied CKD patients during the long-term follow-up and these might affect the renal outcome.

To avoid the confounding factors, a shorter duration of follow-up was employed in the present study. After a 12-week follow-up, the values of blood pressure were excellently controlled, the values of inflammatory markers were in normal range, and the amount of proteinuria was significantly decreased while the serum creatinine and cystatin C levels were significantly elevated (Table 1). The serum calcium, phosphate, and intact PTH levels were unchanged while the values of serum 25-OH vitamin D and FGF-23 were significantly increased (Table 1).

Indeed, FGF-23 is one of the earliest metabolic abnormalities developing in CKD. The FGF-23 levels are progressively increased following the more severity of CKD staging[4,6]. The persistently elevated FGF-23 levels enhance the risks of both mortality and cardiovascular events across the entire spectrum of renal disease[5,7,12,19-22]. Furthermore, there is a near-linear increase in these risks with increasing FGF-23 concentrations[6]. In the last decade, FGF-23 has been proposed to be a potentially reliable marker of renal progression[5,7,9]. Previous studies examined the role of baseline FGF-23 levels on progression of renal function in CKD patients after 2 to 5.5 years follow-up (Table 4). As shown in Figure 1, the delta change of FGF-23 values, between the levels at baseline and at the twelfth week, were progressively elevated following the severity of CKD staging. When the delta change of FGF-23 and eGFR values of each participating CKD patient in the present study were determined, there was a significantly inverse association between delta change of FGF-23 levels and delta change of eGFR values in short-term follow-up (Figure 2).

When the baseline level of each renal progression-associated factor was assessed for correlation with the eGFR value at the twelfth week, the baseline intact PTH level was the only parameter that had significant association with declined renal function (Table 2). However, such baseline intact PTH value was still in the recommended range according to the KDIGO guideline[23]. As such, the baseline PTH is not a suitable biomarker for detecting progression of renal function in clinical practice. Although many of these studies have revealed the positive relationship between the elevated baseline FGF-23 levels and the decline in renal function as well as elevation in incidences of CKD and ESRD[5,7,8,12,24], some studies could not show such association[10,11]. The present study also did not observe the relationship between the baseline levels of FGF-23 and renal function.

To identify the novel parameters in detecting progression of renal function, the delta values of renal progression-associated risk factors were compared with the delta value of eGFR. As shown in Table 3, the delta change of FGF-23 value was the only variable that was correlated with the delta change of eGFR value in both univariate and multivariate linear regression analysis. Taken together, the delta change of FGF-23 value might be more sensitive than the baseline FGF-23 level and might be a more suitable marker than other renal progression-associated risk factors in detecting the progression of renal function in CKD patients.

Accordingly, FGF-23 should be regularly monitored together with other parameters including creatinine, calcium, phosphate, vitamin D, and PTH in CKD patients. Moreover, in patients with increased FGF-23 level the causes should be explored and classified as a high risk of CKD progression. The

Table 4. Summary the association between serum FGF-23 and renal outcomes from previous studies

Authors	Year	Population	FGF-23	Follow-up	Renal outcomes
Fliser, et al.[5]	2007	CKD	Baseline (intact mean 47.5 pg/mL)	4.4 years	Increased risk of doubling of baseline serum creatinine and/or terminal renal failure necessitating renal replacement therapy
Isakova, et al.[24]	2011	CKD	Baseline (C-terminal median 145 RU/mL)	3.5 years	Increased risk of ESRD (only eGFR >30 mL/minute/1.73 m^2)
Kendrick, et al.[7]	2011	CKD	Baseline (C-terminal 392 RU/mL)	2.9 years	Increased risk of ESRD
Wolf, et al.[22]	2011	Kidney transplant	Baseline (C-terminal 28 RU/mL)	3 years	Increased risk of allograft loss
Lundberg, et al.[20]	2012	Chronic IgA nephropathy	Baseline (C-terminal 18.5 RU/mL)	4.6 years	Increased risk of progression to CKD stage 5 or ≥50% loss of eGFR
Nakano, et al.[26]	2012	CKD	Baseline (intact mean 49.5 pg/mL)	4.4 years	Increased risk of doubling of serum creatinine or initiation of dialysis
Levin, et al.[11]	2014	CKD	Baseline (C-terminal 237 RU/mL)	1 years	Non-significant increased risk of ESRD
Bouma-de Krijger, et al.[12]	2014	CKD	Baseline (C-terminal 149 RU/mL)	2 years	Increased risk of ESRD
Tripepi, et al.[21]	2015	CKD	Baseline (intact mean 61 pg/mL)	3 years	Increased risk of decrease in eGFR of >30%, dialysis, or kidney transplantation
Portale, et al.[9]	2016	CKD pediatrics	Baseline (C-terminal 132 RU/mL)	5.5 years	Increased risk of starting dialysis or kidney transplantation or 50% decline from baseline GFR
Shardlow, et al.[10]	2017	CKD	Baseline (intact mean 42.0 pg/mL)	5 years	Not significantly increased risk of renal progression (25% drop of eGFR)
Jialal, et al.[19]	2017	CKD	Baseline (C-terminal 154.1 RU/mL)	3 years	Increased risk of ESRD

FGF-23=fibroblast growth factor-23; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; ESRD=end stage renal disease; GFR=glomerular filtration rate

strictly controlled serum phosphate, vitamin D, and PTH level should also be emphasized to prevent the progression of CKD.

It is well established that FGF-23 is stimulated by 1,25 OH vitamin D[1,25]. In the present study, all participating patients received natural vitamin D supplement (40,000 units weekly of ergocalciferol with or without calcitriol). Of interest, the serum FGF-23 level was simultaneously increased together with the elevation of serum 25-OH vitamin D levels (Figure 3). This significant correlation was independent whether patients received active vitamin D or not. Several previous studies also reported that vitamin D status critically influenced FGF-23 elevation[1-3]. This would underscore the importance of serum vitamin D monitoring in patients with CKD stage 3 to 5 who usually receive vitamin D supplement.

Despite being the first study to demonstrate the significant association between the change of serum FGF-23 and renal function along the follow-up time, there were still certain limitations. Firstly, the time period to follow-up of FGF-23 level was not sufficient for exploring the incidence of starting dialysis and mortality. Secondly, the sample size was rather small, and the participating patients included only patients with CKD stage 3a to 4, and not stage 5. Therefore, using FGF-23 as follow-up marker in pre-dialysis progression of renal function in CKD stage 5 needs further studies.

Conclusion

Increase in serum FGF-23 level is significantly correlated with the decline of renal function. Thus, serum FGF-23 levels could be followed as an appropriate biomarker for predicting CKD progression.

What is already known on this topic?

Baseline FGF-23 levels are independently associated with CKD progression. However, the correlation of the changes of FGF-23 and declination of renal function has not yet been established.

What this study adds?

Increase in serum FGF-23 level is significantly correlated with the decline of renal function. Thus, serum FGF-23 levels could be followed as an appropriate biomarker for predicting CKD progression.

Acknowledgement

The authors would like to thank all the patients for their participation in the present study.

Ethical approval and consent to participate

The present study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (Bangkok, Thailand; IRB.644/59). Written informed consents were obtained from all subjects.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Wahl P, Wolf M. FGF23 in chronic kidney disease. Adv Exp Med Biol 2012;728:107-25.
2. de Borst MH, Vervloet MG, ter Wee PM, Navis G. Cross talk between the renin-angiotensin-aldosterone system and vitamin D-FGF-23-klotho in chronic kidney disease. J Am Soc Nephrol 2011;22:1603-9.
3. Isakova T, Wahl P, Vargas GS, Gutiérrez OM, Scialla J, Xie H, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int 2011;79:1370-8.
4. Chathoth S, Al Mueilo S, Cyrus C, Vatte C, Al Nafaie A, Al Ali R, et al. Elevated fibroblast growth factor 23 concentration: prediction of mortality among chronic kidney disease patients. cardiorenal med 2015;6:73-82.
5. Fliser D, Kollerits B, Neyer U, Ankerst DP, Lhotta K, Lingenhel A, et al. Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) study. J Am Soc Nephrol 2007;18:2600-8.
6. Sharaf El Din UA, Salem MM, Abdulazim DO. Is Fibroblast growth factor 23 the leading cause of increased mortality among chronic kidney disease patients? A narrative review. J Adv Res 2017;8:271-8.
7. Kendrick J, Cheung AK, Kaufman JS, Greene T, Roberts WL, Smits G, et al. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. J Am Soc Nephrol 2011;22:1913-22.
8. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA 2011;305:2432-9.
9. Portale AA, Wolf MS, Messinger S, Perwad F, Jüppner H, Warady BA, et al. Fibroblast growth factor 23 and risk of CKD progression in children. Clin J Am Soc Nephrol 2016;11:1989-98.
10. Shardlow A, McIntyre NJ, Fluck RJ, McIntyre CW, Taal MW. Associations of fibroblast growth factor 23, vitamin D and parathyroid hormone with 5-year outcomes in a prospective primary care cohort of people with chronic kidney disease stage 3. BMJ Open 2017;7:e016528.
11. Levin A, Rigatto C, Barrett B, Madore F, Muirhead N, Holmes D, et al. Biomarkers of inflammation, fibrosis, cardiac stretch and injury predict death but not renal replacement therapy at 1 year in a Canadian chronic kidney disease cohort. Nephrol Dial Transplant 2014;29:1037-47.
12. Bouma-de Krijger A, Bots ML, Vervloet MG, Blankestijn PJ, Ter Wee PW, van Zuilen AD, et al. Time-averaged level of fibroblast growth factor-23 and clinical events in chronic kidney disease. Nephrol Dial Transplant 2014;29:88-97.
13. van d, V, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int 2011;79:1341-52.
14. Nagai K, Sairenchi T, Irie F, Watanabe H, Ota H, Yamagata K. Relationship between estimated glomerular filtration rate and cardiovascular mortality in a Japanese cohort with long-term follow-up. PLoS One 2016;11:e0156792.
15. Moradi H, Sica DA, Kalantar-Zadeh K. Cardiovascular burden associated with uremic toxins in patients with chronic kidney disease. Am J Nephrol 2013;38:136-48.
16. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension 2003;42:1050-65.
17. Kendrick J, Chonchol MB. Nontraditional risk factors for cardiovascular disease in patients with chronic kidney disease. Nat Clin Pract Nephrol 2008;4:672-81.
18. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet 2013;382:339-52.
19. Jialal I, Camacho F, Nathoo B, Tam P, Pahwa R, Wu GG. Fibroblast growth factor 23 predicts mortality and end-stage renal disease in a Canadian Asian Population with chronic kidney disease. Nephron 2017;137:190-6.
20. Lundberg S, Qureshi AR, Olivecrona S, Gunnarsson I, Jacobson SH, Larsson TE. FGF23, albuminuria, and disease progression in patients with chronic IgA nephropathy. Clin J Am Soc Nephrol 2012;7:727-34.
21. Tripepi G, Kollerits B, Leonardis D, Yilmaz MI, Postorino M, Fliser D, et al. Competitive interaction between fibroblast growth factor 23 and asymmetric dimethylarginine in patients with CKD. J Am Soc Nephrol 2015;26:935-44.
22. Wolf M, Molnar MZ, Amaral AP, Czira ME, Rudas A, Ujszaszi A, et al. Elevated fibroblast growth factor 23 is a risk factor for kidney transplant loss and mortality. J Am Soc Nephrol 2011;22:956-66.
23. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 2009;(113):S1-130.
24. Isakova T, Craven TE, Lee J, Scialla JJ, Xie H, Wahl P,

et al. Fibroblast growth factor 23 and incident CKD in type 2 diabetes. Clin J Am Soc Nephrol 2015;10:29-38.
25. Taal MW, Thurston V, McIntyre NJ, Fluck RJ, McIntyre CW. The impact of vitamin D status on the relative increase in fibroblast growth factor 23 and parathyroid hormone in chronic kidney disease. Kidney Int 2014;86:407-13.
26. Nakano C, Hamano T, Fujii N, Obi Y, Matsui I, Tomida K, et al. Intact fibroblast growth factor 23 levels predict incident cardiovascular event before but not after the start of dialysis. Bone 2012;50:1266-74.