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Correlation of glomerular filtration rate and fibroblast growth factor-23 levels in chronic kidney disease; sub analysis chronic kidney disease–mineral and bone disorder study

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ABSTRACT

Introduction: One of the chronic kidney disease (CKD) manifestations is mineral disorder, such as phosphate and calcium. Phosphatonin levels are regulated by the hormone phosphatonin, which the most commonly associated with CKD is fibroblast growth factor-23 (FGF-23), mainly synthesized by bone cells. The increase in FGF-23 in CKD subjects is a physiological response to stabilize phosphate levels. Several conditions can increase FGF-23 levels including age, body mass index (BMI), diabetes mellitus (DM), and hypertension.

Objectives: This study aims to test the correlation between FGF-23 levels at various stages of glomerular filtration rate (GFR) in CKD.

Patients and Methods: This study is observational with a cross-sectional approach conducted at Wahidin Sudirohusodo and Unhas hospitals of Makassar. Subjects are CKD patients which meet inclusion criteria. Intact serum FGF-23 levels were measured using an ELISA (enzyme-linked immunosorbent assay) kit (Immutopics). Statistical analysis was conducted using ANOVA test, Mann-Whitney U, and Spearman's correlation tests. Statistical results are considered significant if $P<0.05$.

Results: The research was conducted on 78 subjects with CKD stages 3, 4 and 5, which consisted of 40 men and 38 women. The correlation test showed that the lower the GFR, the higher the FGF-23 level ($P<0.05$). No significant correlation between age, body mass index, diabetes mellitus, and hypertension with FGF-23 were detected ($P>0.05$).

Conclusion: We found that every increase in the CKD stages and decrease of GFR, would be associated with an increase in the plasma levels of FGF-23. However, FGF-23 plasma concentration had no significant correlation with age, BMI, DM, and hypertension.

Implication for health policy/practice/research/medical education:
Increased FGF-23 level in chronic kidney disease patients is a physiological response to stabilize phosphate levels through increased urinary phosphate excretion. FGF-23 has the potential to be a novel, easily quantifiable biomarker for a strong prognostic predictor of mortality in chronic kidney disease. However, this measurement is still very limited and expensive; that becomes one of the weaknesses when conducted in daily practice.

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Introduction

According to Kidney Disease Quality Outcome Initiative (K/DOQI), chronic kidney disease (CKD) is defined as structural damage or functional disorder of the kidney for 3 months or more, irrespective of cause (1). Kidney damage and functional disorder can be ascertained by the presence of one or more of the following findings; albuminuria (albumin excretion rate >30 mg/24 h; albumin to creatinine ratio >30 mg/g), urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders abnormalities detected by histology, structural abnormalities detected by imaging, history of

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kidney transplantation, and eGFR (estimated glomerular filtration rate) ≤ 60 mL/min/1.73 m^2 (1,2).

One of the CKD manifestations is mineral disorder, such as phosphate and calcium. The total adult body store of phosphorus is approximately 700 g, containing 85% in bone in the form of hydroxyapatite [$(Ca)_{10}(PO_4)_6(OH)_2$]. Of the remaining, 14% is intracellular, and only 1% is extracellular. The extracellular phosphorus is 70% in organic form and 30% in inorganic form. About 15% of extracellular phosphorus is in the circulation, called phosphate, which can be measured in the plasma (2).

Small intestine, kidneys, and bones are the organs controlling the homeostasis of phosphorus. Phosphate levels are controlled by vitamin D and parathyroid hormone (PTH). In several studies, phosphate levels are regulated by phosphatonin hormone, and fibroblast growth factor 23 (FGF-23) which are associated with CKD the most. Inorganic phosphorus is almost entirely (70%-89%) filtered at the glomerulus and reabsorbed in the proximal tubule, while 20%-30% is reabsorbed in the distal tubule. A factor that increases the excretion of phosphate is increased plasma phosphate concentration. On the other hand, if there is phosphate depletion, there will be a decrease in excretion. At GFR 50 mL/min/1.73 m2, the ability of the kidneys to excrete phosphate begins to decrease, however phosphate levels remain in the normal range of 2.5-4.5 mg/dL. Increased phosphate level will stimulate PTH secretion and increases the synthesis and secretion of FGF-23 levels from the bone. Increased expression of FGF-23 in osteocytes occurs early in the course of CKD, where circulating FGF-23 levels have been elevated in 30%-40% of adult subjects with a GFR of 70-90 mL/min/1.73 m^2. FFurthermore, FGF-23 will increase phosphate excretion, causing the plasma phosphate level returning to normal. Additionally, hyperphosphatemia will occur in the later stages of CKD (GFR <30 mL/min/1.73 m^2) (2,3).

FGF-23 is a protein that is mainly synthesized by bone cells; primarily by osteoclasts, while a small amount by osteoblasts, and others are synthesized in various other body organs. The primary function of FGF-23 in the kidneys in healthy subjects is to regulate urinary phosphate excretion when there is an increase in phosphate intake to maintain phosphate levels in a stable normal range. However, epidemiological studies have shown no evidence of the association between FGF-23 levels and serum phosphate levels in individuals without impaired renal function. The increase in FGF-23 in CKD subjects is a physiological response to stabilize phosphate levels by increasing the excretion of phosphate in the urine, by decreasing the expression of NaPi-Iia and NaPi-Iic co-transporter in the kidney. The elevation of FGF-23 decreases phosphate reabsorption and NaPi-IIb co-transporter in the small intestine therefore, the absorption of phosphate in the small intestine subsequently decreases. FGF-23 also reduces phosphate absorption in the small intestine indirectly by inhibiting 1-alpha hydroxylase and decreasing calcitriol levels (4,5).

The effect of FGF-23 occurs when FGF-23 binds to klotho as a co-receptor to form a co-receptor complex FGF-23 klotho (3). Studies by Gutierrez et al (6), Marsel et al (7), and Flisser et al (8) found evidence that FGF-23 levels increased along with decreased kidney function. Elevated FGF-23 levels are also associated with cardiovascular events, left ventricular hypertrophy, and progression of CKD (4,5).

In non-CKD patients, several conditions can increase FGF-23 levels such as; age, obesity, hypertension, and diabetes mellitus (DM) (9-12).

Objectives

Knowing the correlation between GFR and FGF-23 levels and the factors that affect FGF-23 levels can be a reference as one of the prognostic parameters for the course of CKD and can be used as a reference for further research.

Patients and Methods

Study design

This study was designed with observational research with a cross-sectional approach. Subjects were recruited in outpatient and inpatient department of Wahidin Sudirohusodo hospital with the diagnosis of stage 3, 4, and 5 CKD who received hemodialysis and non-hemodialysis therapy between April and August 2021. The inclusion criteria were patients with age >18-65 years, diagnosed with CKD, not consuming any phosphate binders, and willing to participate in research and sign informed consent. Intact serum FGF-23 levels were measured using an enzyme immunoassay kit.

Laboratory analysis

Sampling is done by consecutive sampling. Blood sampling was conducted by taking blood with a 5-cc disposable syringe and serum separator tube and then covering the puncture mark with plaster. The tube is turned back and forth 5-10 times until homogeneous, then allowed to stand for 30-45 minutes until the blood is frozen, then centrifuged 1000× for 15 minutes. The serum is separated and put into three up samples each 0.5 cc of serum (labeled with identity, name, and date), then frozen and stored -20°C. Serum levels of (C-Term) FGF-23 were measured using an FGF-23 enzyme immunoassay (ELISA) kit (Immunotopics Inc, San Clemente, USA) according to the manufacturer's instructions.

Determination of CKD stage

The grading of renal function as stage of CKD from G3 to G5 based on estimated glomerular filtration rate (eGFR) level or the indication for renal replacement therapy, in this case hemodialysis. Calculation of eGFR was using equation of chronic kidney disease – epidemiology collaboration (CKD-EPI) that eGFR (mL/min/1.73 m^2) =

141 * min (Scr/κ,1)α * max (Scr/κ, 1)-1.209 * 0.993 Age * 1.018 [if female] * 1.159 [if black]; with Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. After that, the stage is determined by G3 (eGFR 30–59 mL/min/m^2); G4 (eGFR 15–29 mL/min/m^2); and G5 (eGFR <15 mL/min/m^2).

Statistical analysis

Data analysis was conducted using SPSS version 25. The method of analysis consisted of descriptive methods and statistical tests. The descriptive method aims to obtain general information about the research sample. Statistical tests include calculation of the mean value and standard deviation (SD) and the frequency distribution, using ANOVA, Mann-Whitney U, and Spearman's rho tests. The results were considered significant if the *P* value was <0.05. The results are displayed in the following narration, with tables and pictures.

Results

Characteristics of research subjects

The study was conducted with 78 subjects with CKD stages 3, 4, and 5 consisting of 40 men (51.3%) and 38 women (48.7%) with a mean age of 48.5 ± 12.5 years. The youngest is 18 years old and the oldest is 65 years old. There were 19 subjects (24.2%) in the obese category based on their body mass index (BMI) and 59 subjects (75.6%) in non-obese. The lowest BMI was 15.4 kg/m^2 and the highest was BMI 34.6 kg/m^2 with a mean BMI of 22.7 ±3.6 kg/m^2. FGF-23 levels were at minimum of 12.3 RU/mL and maximum of 2013.2 RU/mL with the average of 387.9±423.5 RU/mL. There were 42 (53.8%) subjects with hypertension and 36 (46.2%) without hypertension. There were 30 (38.5%) subjects with DM and 48 (61.5%) without DM (Table 1).

Table 1. Characteristics of research subjects

Variable	n	%
Gender		
Man	40	51.3
Women	38	48.7
Age (y)		
>60	14	17.9
≤60	64	82.1
BMI (kg/m^2)		
Obese	19	24.4
Non-obese	59	75.6
Hypertension		
With	42	53.8
Without	36	46.2
DM		
With	30	38.5
Without	48	61.5

Average FGF-23 levels based on CKD stage

The average level of FGF-23 based on the CKD stage showed an increase in the FGF-23 level at every increase in the CKD stage. The more severe the degree of CKD, the more significantly higher the FGF-23 level ($P<0.001$). Table 2 and Figure 1 present the analysis results of the average levels of FGF-23 based on the CKD stage.

Results

Characteristics of research subjects

The study was conducted with 78 subjects with CKD stages 3, 4, and 5 consisting of 40 men (51.3%) and 38 women (48.7%) with a mean age of 48.5 ± 12.5 years. The youngest is 18 years old and the oldest is 65 years old. There were 19 subjects (24.2%) in the obese category based on their body mass index (BMI) and 59 subjects (75.6%) in non-obese. The lowest BMI was 15.4 kg/m^2 and the highest was BMI 34.6 kg/m^2 with a mean BMI of 22.7 ± 3.6 kg/m^2. FGF-23 levels was at minimum of 12.3 RU/mL and maximum of 2013.2 RU/mL with the average of 387.9 ± 423.5 RU/mL. There were 42 (53.8%) subjects with hypertension and 36 (46.2%) without hypertension. There were 30 (38.5%) subjects with DM and 48 (61.5%) without DM.

Our further analysis using multiple comparisons of the mean FGF-23 levels based on the CKD stage showed that stage three is not significantly different from stage 4 ($P=0.822$). Meanwhile, the mean FGF-23 levels comparison at other stages is significantly different (Table 3).

Correlation between GFR and FGF-23 levels

The correlation between GFR and FGF-23 levels at CKD

Table 2. Average FGF-23 levels based on CKD stage

Stage	FGF-23 Levels			*P**
	N	Mean ± SD (RU/mL)	95% CI	
3	19	110±141.1	41.9-177.9	<0.0001
4	19	134.1±161.4	56.3-211.9	
5 Non-dialysis	20	528.5±513.6	288.1-768.9	
5 Dialysis	20	752.3±342.3	592.1-912.5	

*ANOVA test.

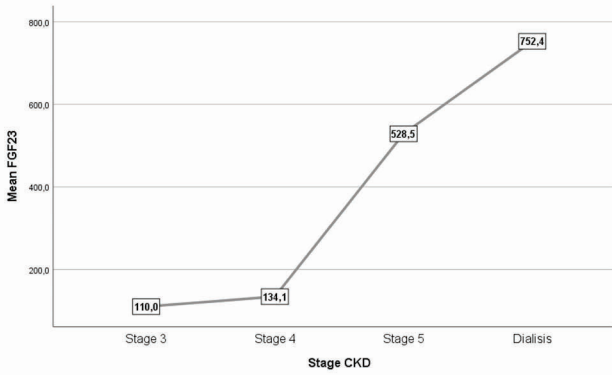

Figure 1. Mean FGF-23 in CKD stage.

Table 3. Comparison of mean FGF-23 levels based on CKD stage

Staging CKD	Staging CKD	Differences in the mean levels of FGF-23	95% CI		*P* value*
			Lower bound	Upper bound	
3	4	-24.2	-237.612	189.276	0.822
	5 Non-dialysis	-418.6	-629.330	-207.812	<0.0001
	5 Dialysis	-642.4	-853.140	-431.622	<0.0001
4	3	24.2	-189.276	237.612	0.822
	5 Non-dialysis	-394.4	-605.162	-183.644	<0.0001
	5 Dialysis	-618.2	-828.972	-407.454	<0.0001
5 Non-dialysis	3	418.6	207.812	629.330	<0.0001
	4	394.4	183.644	605.162	<0.0001
	5 Dialysis	-223.8	-431.850	-15.770	0.035
5 Dialysis	3	642.4	431.622	853.140	<0.0001
	4	618.2	407.454	828.972	<0.0001
	5 Non-dialysis	223.8	15.770	431.850	0.035

*LSD, the mean difference is significant if $P < 0.05$.

stage 5 dialysis subjects were not analyzed because, at this stage, the dialysis process influenced the GFR calculation. From non-dialysis stages 3, 4 and 5 CKD subjects (n=58), there was a significant negative correlation between GFR and FGF-23 levels, where the lower the GFR, the higher the FGF-23 levels (R=-0.583; $P = 0.0001$; Figure 2).

Correlation between age, BMI, DM, and hypertension with mean FGF-23 levels in CKD

Since FGF-23 levels are affected by age, BMI, DM and hypertension, we further analyze whether there is a correlation with FGF-23. Accordingly, we found no significant correlation between age, BMI, DM and hypertension with FGF-23 ($P > 0.05$; Table 4).

Discussion

This study aims to assess the correlation between GFR and FGF-23 levels. According to the KDOQI, the diagnosis of advanced CKD based on GFR is when the GFR is <60 mL/min/1.73 m^2, which includes stages 3, 4, and 5 (13). Until now, there is no normal cut-off for FGF-23 levels, therefore we used mean FGF-23 levels (4). FGF-23 levels increase progressively with decreasing GFR at stage 3 (GFR <60 mL/min/1.73 m^2) (14), thereby we took samples at stage 3.

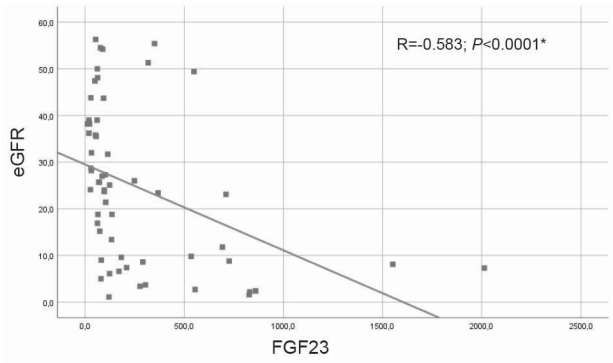

Figure 2. Correlation between GFR and FGF-23 levels in CKD (n=58). *Spearman's correlation test.

The non-phosphate uric effect of FGF-23 is associated with cardiovascular events, such as left ventricular hypertrophy, endothelial dysfunction, and atherosclerosis. Accordingly, the increased levels of FGF-23 can also be associated with the increased risk of mortality due to cardiovascular events (15).

Analysis of the mean levels of FGF-23 based on the CKD stage in this study showed an increase in FGF-23 levels at each increase in the CKD stage. The increase in the degree of CKD is associated with significantly higher FGF-23 levels ($P < 0.0001$), with FGF-23 levels in stage 3 at 110 RU/mL, stage 4 at 134.1 RU/mL, and stage 5 non-dialysis at 528.5 RU/mL, and finally stage 5 dialysis at 752.4 RU/mL (Table 2 and Figure 1). These results are in line with the previous research from Pavik et al (16), Gutierrez et al (6), and Tanaka et al (17), who found that the higher

Table 4. Correlation between age, BMI, DM, and hypertension with mean FGF-23 levels in CKD

Variable	n	Mean±SD (RU/mL)	*P* value*
Age			
>60 years	14	427.8 ± 444.4	0.223
≤60 years	64	205.7 ± 248.5	
BMI (kg/m^2)			
Obese	19	349.8 ± 427.4	0.526
Non-obese	59	400.15 ± 425.1	
Hypertension			
With	42	403.9 ± 389.4	0.370
Without	36	369.2 ± 465.1	
DM			
With	30	338.4 ± 382.8	0.531
Without	48	418.8 ± 448.2	

*Mann-Whitney U test.

the CKD stage, is correlated with the higher the FGF-23 levels.

In the study by Pavik et al (16) that examined 87 subjects, there were differences in the mean levels of FGF-23 at each stage of CKD (stages 1-5 CKD respectively: 54.3 RU/mL; 65.1 RU/mL; 137.7 RU/mL; 377.2 RU/mL; 120.6 RU/mL). This increase in FGF-23 levels is associated with resistance to FGF-23 at each progression of CKD stages while klotho, which is a co-receptor of FGF-23, decreases as the degree of CKD increases that the level of FGF-23 bound to klotho decreases, or in other words, the level of free FGF-23 increases (18).

The study by Gutierrez et al (6) divided the subjects into four groups: [1] GFR > 60, [2] 45-60, [3] 30-45, [4] < 30 mL/min/1.73 m^2. The levels of FGF-23 for each respective group were 86.2± 61.4, 136.2 ± 69.1, 224.6 ± 200.1 and 436.0 ± 493.8 RU/mL. Meanwhile, in a study by Tanaka et al (17) with 903 patients with various groups of subjects with stage 1 to 5 CKD, it was found that the third tertile was significantly higher in each of the more severe stages of CKD ($P<0.001$), meaning that FGF-23 increased with decreasing kidney function. This observation occurred because of the resistance of FGF-23 in the nephron, and this resistance to FGF-23 is associated with CKD progression at each stage (18).

Using multiple comparisons, this study found that although FGF-23 levels were higher at stage 4 than stage 3, it was not statistically significant ($P=0.822$). Meanwhile, the comparison of the FGF-23 mean levels at stage 5 non-dialysis was significant. Results for stage 5 dialysis were significantly higher than stage 5 non-dialysis and results for both stage 5 dialysis and non-dialysis are also higher than stage 3 and stage 4 (Table 3). The heterogeneous distribution of FGF-23 levels at each stage of CKD is thought to be a combination of genetics, the severity of CKD, and modifiable components such as phosphorus intake (19).

The circulating levels of FGF-23 in CKD patients increase gradually with decreasing GFR. Fliser et al (8) in their study also divided 227 patients into four groups; (1) GFR >90 , (2) 60-89, (3) 30-59, (4) < 30 mL/min. Each obtained levels of 57 ± 43 RU/ mL; 81 ± 52 RU/mL; 187 ± 194 RU/mL and 456 ± 475 RU/mL respectively. In line with the study by Fliser et al (8), our findings showed a significant negative correlation between GFR and FGF-23 levels in CKD, where the lower the GFR, the higher FGF-23 levels (R=-0.583; $P=0.0001$; Figure 2). However, in our study, subjects for stage 5 dialysis are excluded (n=20 excluded, n=58 included), because at this stage GFR was affected by dialysis.

FGF-23 levels increase with each decrease in GFR as a physiological compensation to stabilize serum phosphate levels because the number of intact nephrons decreases (20).

Several factors can affect FGF-23 levels, such as age, BMI, DM, and hypertension. Nevertheless, in our study, there was no difference in the mean FGF-23 levels based on age, BMI, DM, and hypertension ($P>0.05$; Table 4).

Likewise, Souma et al (21) examined 2525 subjects and found that the highest tertile of FGF-23 levels was in the age group >60 years with a mean age of 68.9 ± 9.9 years. Speer et al (22) studied 859 subjects and also found that patients in the highest FGF-23 tertile tend to be older, with a mean age of 63.7 years. There was no correlation between age and FGF-23 levels in our study due to differences in metabolic status in the study subjects, while changes in metabolic status generally occur with increasing age, which these changes are different for each individual (15).

Previously, Hu et al (9) studied 1599 subjects and found serum levels of FGF-23 significantly increased in obese subjects. In an agreement with the study of Gutierrez et al (23) who examined 1261 subjects, we found that FGF-23 levels were significantly higher in obese than non-obese subjects. As our study used simple parameters, we considered the difference with other studies is due to a different measurement method. Increased levels of FGF-23 in obese subjects were associated with fat content and fat distribution (visceral and subcutaneous) as measured using magnetic resonance imaging or bio-impedance analyzer (9).

Diabetes causes a decrease in the rate of bone formation, thereby stimulating the secretion of FGF-23. A study by Wahl et al (24) with 1,936 non-DM subjects and 1820 DM subjects found a significant result of high FGF-23 levels in the DM group. The difference in result is considered due to the small sample size conducted in our study and the use of medication that affects mineral metabolism in the study by Wahl et al.

Gutierrez et al (23) also found that 1,261 hypertensive subjects had higher FGF-23 levels than the non-hypertensive group. However, our study showed no correlation between hypertension and FGF-23 levels which possibly may be due to the genetic factors that were not included in this study.

Conclusion

In conclusion, the lower the GFR, the higher the FGF-23 levels. There is an increase in FGF-23 levels with each increase in the CKD stage. Our study showed no significant correlation between age, BMI, DM and hypertension with plasma FGF-23. We provided evidence that FGF-23 has the potential to be a novel, easily quantifiable biomarker for a strong prognostic predictor of outcome in CKD. However, further examination is necessary to compare FGF-23 levels at each stage of CKD with healthy subjects.

Limitations of the study

There was no definition of normal cut-off for FGF-23 levels that led to differences in mean FGF-23 levels.

Authors' contribution

AST, HR, SB, and HK were the principal investigators

of the study and drafted the manuscript; AST and AS collected and analyzed the data; TH, HI, and MLP contributed to the concept and design of the study; HR and SB revisited the manuscript and critically evaluated the intellectual contents. All authors participated in the final draft preparation, manuscript revision, and critical evaluation of the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research was conducted following the tenets of the Declaration of Helsinki. The ethics committee for clinical research of Faculty of medicine Hasanuddin University and Dr. Wahidin Sudirohusodo hospital Makassar approved this study. The institutional ethical committee at the faculty of medicine Hasanuddin university accepted all study protocols (Ref#219/UN4.6.4.5.31/PP36/2021). Accordingly, written informed consent was taken from all participants. Besides, the authors have observed all ethical issues (including plagiarism, data fabrication and double publication).

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